

# An analysis of 342 patients with refractory gastroesophageal reflux disease symptoms using questionnaires, high-resolution manometry, and impedance-pH monitoring

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## Abstract

Symptoms of refractory gastroesophageal reflux disease (GERD) are commonly encountered in clinical practice. The aim of this study was to analyze the data obtained from questionnaires, high-resolution manometry (HRM), and ambulatory impedance-pH monitoring in patients with persisting GERD symptoms and to explore the possible underlying causes for this clinical presentation. After completing the questionnaires, the selected patients underwent endoscopy, HRM, and ambulatory impedance-pH monitoring. Based on the results of these investigations, we divided the patients into 4 groups: reflux esophagitis (RE), hypersensitive esophagus (HE), functional heartburn (FH), and nonerosive gastroesophageal reflux disease (NERD). The data from 342 patients were analyzed. One hundred twenty-nine (37.72%) patients experienced refractory GERD symptoms related to acid reflux. The scores on some scales in the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire differed significantly among groups (all  $P < 0.05$ ). Liquid reflux occurred more frequently in patients with GERD (RE and NERD), while gas reflux was more common in non-GERD patients (FH and HE; all  $P < 0.05$ ). The RE and NERD groups showed more percent bolus exposure time (BET) when upright (all  $P < 0.05$ ). Acid exposure time (AET) in the RE and NERD groups was longer than that in the HE and FH groups (all  $P < 0.05$ ). Fewer than half of the patient symptoms were related to acid reflux. The GSRS questionnaire may be an optimal indicator for patients with refractory GERD symptoms. BET and AET are useful indices to distinguish GERD from other diseases. Gas reflux is probably related to persisting symptoms in FH and HE patients.

**Abbreviations:** AET = acid exposure time, BET = bolus exposure time, CFV = contractile front velocity, DES = diffuse esophageal spasm, DCI = distal contractile integral, FH = functional heartburn, GERD = gastroesophageal reflux disease, GERD-HRQL = GERD-health-related quality of life, GSRS = Gastrointestinal Symptom Rating Scale, HE = hypersensitive esophagus, HH = hiatal hernia, HRM = high-resolution manometry, LES = lower esophageal sphincter, LESPI = lower esophageal sphincter pressure integral, NERD = nonerosive gastroesophageal reflux disease, PPI = proton pump inhibitor, RE = reflux esophagitis, UES = upper esophageal sphincter.

**Keywords:** gastroesophageal reflux disease, high-resolution manometry, impedance-pH monitoring, questionnaire survey, refractory proton pump inhibitor symptoms

Editor: Gabrio Bassotti.

Author contribution: FW, PL, and XC carried out the research; FW and XC analyzed the data and wrote the paper; G-ZJ, LM, ZF, and XC designed the research study. SY and XP contributed to the management of patients.

Funding/support: This work was partly funded by Nanjing City Medical Science and Technology Development Program (YKK13180) and by the 10th of 6 talent peak program in Jiangsu province (2013-WSN-052).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:5(e5906)

Received: 26 October 2016 / Received in final form: 12 December 2016 /

Accepted: 27 December 2016

<http://dx.doi.org/10.1097/MD.0000000000005906>

## 1. Introduction

Gastroesophageal reflux disease (GERD) is related to a wide range of symptoms that severely impair health-related quality of life (HRQL). Proton pump inhibitors (PPIs) have been universally accepted as first-line therapy for the management of GERD. However, troublesome GERD symptoms persist in 20% to 30% of patients despite daily treatment with a standard PPI dose.<sup>[1]</sup> Furthermore, it has been reported that the PPI responsiveness in patients with nonerosive gastroesophageal reflux disease (NERD) is less than 60%.<sup>[2]</sup>

Certain functional esophageal disorders also present similar reflux symptoms and may cause refractory GERD symptoms. It is therefore necessary to accurately diagnose refractory GERD symptoms in order to avoid unnecessary PPI therapy and to guide appropriate management. The American College of Gastroenterology has recommended that patients with PPI-refractory reflux symptoms be evaluated while receiving PPI therapy.<sup>[3]</sup> High-resolution manometry (HRM) and impedance-pH monitoring can establish whether refractory symptoms are due to reflux and therefore aid precise diagnosis.

The aims of this study were to present the demographic characteristics of patients with refractory GERD symptoms in

China and to analyze the data obtained from questionnaires, HRM, and ambulatory impedance-pH monitoring. The data obtained were also used to diagnose other diseases and were compared among disease groups in order to figure out the possible underlying causes for refractory GERD symptoms.

## 2. Methods

### 2.1. Patients

This study included patients with refractory GERD symptoms persisting after 8 weeks of standard PPI therapy (single dose daily). The patients had ceased PPI therapy at least 2 weeks before included. Patients were evaluated by upper gastrointestinal endoscopy to identify reflux esophagitis (RE) and other organic abnormalities. Patients with organic disease of the digestive tract and/or previous surgery, significant comorbidities, or functional gastrointestinal disorders were excluded from the study. The patients underwent HRM and ambulatory 24-hour impedance-pH monitoring after stopped taking relevant drugs in order to eliminate the influence of drugs. The protocol for the research project were approved by the Second Affiliated Hospital of Nanjing Medical University Institutional Ethics Committee within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

### 2.2. Esophageal manometry

All patients underwent impedance HRM (Given Imaging; Los Angeles, CA). The lower esophageal sphincter (LES) pressure, lower esophageal sphincter pressure integral (LESPI), distal contractile integral (DCI), contractile front velocity (CFV), upper esophageal sphincter (UES), and the presence of motility disorders in each subject were assessed with ten 5-mL saline swallows.<sup>[4]</sup> All manometric analyses were carried out with software (Mano View software, Sierra Scientific Instrument Inc; Los Angeles, CA) as previously described by Pandolfino.<sup>[5]</sup> Esophageal movement disorders and dynamic disturbances were assessed and classified according to the Chicago classification.<sup>[6,7]</sup> The data were evaluated according to previously published criteria.<sup>[8,9]</sup>

### 2.3. Ambulatory 24-hour multichannel impedance-pH monitoring

The combined pH-impedance assembly (Given Imaging) was positioned with the proximal pH electrode 5 cm above the LES based on preliminary stationary esophageal manometry. Impedance was measured at 3, 5, 7, 9, 15, and 17 cm above the LES. Patients were asked not to lie down during the daytime, but only at their usual bedtime, and were instructed to have 3 meals and 2 beverages at fixed times. Event markers recorded occurrence of symptoms, meal times, and postural changes. Data were analyzed by using pH Analysis software (Mano View software, Sierra Scientific Instrument Inc).

*Acid reflux* refers to refluxed gastric juice with a pH < 4, which can either reduce the pH of the esophagus to below 4 or occur when the esophageal pH is already below 4. *Weakly acidic reflux* describes reflux events that result in an esophageal pH between 4 and 7, where the pH falls by at least 1 unit, but does not fall below 4. *Nonacid reflux* is reserved for reflux episodes during which no change in pH or pH fall of less than 1 pH unit.<sup>[10]</sup>

### 2.4. Questionnaire survey

GERD-HRQL, Frequency Scale for the Symptoms of GERD, and Gastrointestinal Symptom Rating Scale (GSRS) questionnaires were used to evaluate symptoms and quality of life, as previously published.<sup>[11–15]</sup>

### 2.5. Classification of patients

Patients were classified into 4 groups based on the results of their endoscopic findings, HRM and ambulatory pH monitoring: RE, hypersensitive esophagus (HE), functional heartburn (FH), and NERD. RE was diagnosed using the Los Angeles criteria.<sup>[16]</sup> NERD was defined as negative endoscopic findings in the presence of pathological reflux (DeMeester Score  $\geq 14.72$  or % of total period pH below 4  $\geq 4.45\%$  in ambulatory pH monitoring). HE was defined as having normal acid exposure and positive symptom association as defined by symptom index  $\geq 50\%$  or symptom association probability  $>95\%$ .<sup>[17]</sup> FH was defined as the presence of the same heartburn symptoms as those caused by GERD but without any evidence of abnormal esophageal acid exposure, physiological acid reflux exposure that highly correlates with symptoms or recognized esophageal motility disorders.<sup>[18]</sup>

### 2.6. Statistical analysis

Manual data analysis was performed independently by 2 blinded investigators. The data are presented as mean  $\pm$  standard deviation unless otherwise specified. Statistical analysis included the Pearson chi-square test for categorical variables and analysis of variance for continuous variables. All statistical calculations were performed using SPSS 13.0 (IBM, Chicago, IL). A  $P < 0.05$  was considered significant, and all reported  $P$  values are 2-sided.

## 3. Results

### 3.1. Demographic and clinical characteristics

From October 1, 2010 to October 31, 2015, a total of 342 patients (151 men and 191 women, mean age  $50.1 \pm 18.4$  years) were included in this study. Thirty-five patients (10.23%) were found to have RE on upper gastrointestinal endoscopy (we excluded eosinophilic esophagitis based on pathological diagnosis). The duration of symptoms for these patients was  $4.51 \pm 0.93$  years. There were 204 (59.65%) patients with heartburn, 195 (57.02%) with regurgitation, and 155 (45.32%) with retrosternal discomfort and pain (Table 1). A total of 296 patients were divided into 4 groups: RE (n = 35, 11.82%), NERD (n = 94, 31.76%), FH (n = 104, 35.14%), and HE (n = 63, 21.28%).

### 3.2. Esophageal manometry

Esophageal manometry identified 37 (10.82%) patients with achalasia, 12 (3.51%) with weak peristalsis, 6 (1.75%) with hypertensive esophageal dysmotility, 3 (0.88%) with diffuse esophageal spasm (DES), 56 (16.37%) with hiatal hernia (HH), and 42 (12.28%) with high UES pressure. A total of 167 (48.83%) patients had near-normal results, and 75 (21.93%) patients had low LES pressure (Fig. 1). We compared the data obtained from the 296 patients in the 4 groups (Table 2). The rates of HH, absent and weak peristalsis, and failed swallows were higher in the RE group (all  $P < 0.05$ ). There was no difference in LES length and CFV value among groups (all  $P > 0.05$ ).

**Table 1**  
**Demographics and clinical characteristics.**

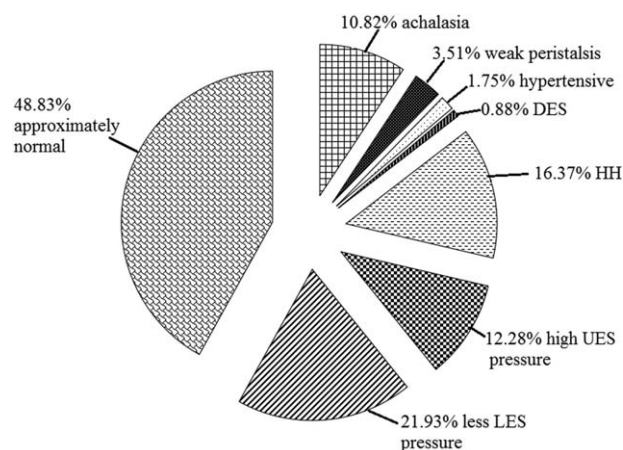
Characteristics (n=342)	n	%
Age, y	50.1 ± 18.4	
Range	19–82	
Gender		
Male	151	44.15
Female	191	55.85
BMI	23.16 ± 9.12	
Endoscopy		
RE	35	10.23
Nonerosive	307	89.77
Smoking	112	32.75
Alcohol consumption	183	53.51
Drug history		
Calcium ion antagonist	142	36.26
Aspirin	104	30.41
Psychotropic drug	43	12.57
Past medical history	225	
Symptom		
Duration, y	4.51 ± 0.93	
Heartburn	204	59.64
Regurgitation	195	57.02
Retrosternal discomfort and pain	155	45.32
Cough	73	21.35
Asthma	16	4.68
Hoarseness	28	8.19
Throat discomfort	155	45.32
Foreign body sensation in throat	98	28.65
Globus sensation	56	16.37
Belching	172	50.29
Dysphagia	123	35.96
Epigastric pain and epigastric discomfort	158	46.20

BMI = body mass index, RE = reflux esophagitis.

However, basal LES pressure, LESPI, DCI, and basal UES pressure in the RE and NERD groups were lower than in the HE and FH groups (all  $P < 0.05$ ). No difference in these values was seen between the HE and FH groups (all  $P > 0.05$ ). In those patients with RE, the values of LES, LESPI, and DCI were lower than in the NERD group (all  $P < 0.05$ ).

### 3.3. 24-Hour impedance-pH monitoring

Acid reflux occurred more frequently in patients with RE than in the other patients while in the upright and recumbent positions and after meals (all  $P < 0.05$ ). It is notable that patients in the



**Figure 1.** Among a total of 342 patients, 37 (10.82%) patients were found with achalasia, 12 (3.51%) with weak peristalsis, 6 (1.75%) with hypertensive, 3 (0.88%) with diffuse esophageal spasm, 56 (16.37%) with hiatal hernia, 42 (12.28%) patients with high upper esophageal sphincter pressure. A total of 75 (21.93%) patients had less lower esophageal sphincter pressure and 167 (48.83%) patients appeared approximately normal results of esophageal manometry.

NERD group had higher values of acid reflux than those in the HE and FH groups (all  $P < 0.05$ ). Conversely, RE patients had the lowest occurrence of weakly acid reflux under all conditions tested (all  $P < 0.05$ ). Differences in nonacid reflux among the 4 groups were not found (all  $P > 0.05$ ). The type of reflux varied between groups, with liquid reflux occurring more frequently in patients with GERD (RE and NERD) and gas reflux more frequently in non-GERD patients (FH and HE) (all  $P < 0.05$ ). Mixed reflux occurred more frequently in RE than in the other groups ( $P < 0.05$ ). Meanwhile, RE and NERD showed more percent bolus exposure when upright, while RE patients experienced more bolus exposure post meals (all  $P < 0.05$ ). RE and NERD scored higher on the DeMeester score compared to the other groups (all  $P < 0.05$ ), and RE patients had a higher level than NERD patients ( $P < 0.05$ ). Acid exposure time in the RE and NERD groups was higher than in the HE and FH groups in 3 varied situations (all  $P < 0.05$ ) (Table 3).

### 3.4. Questionnaire survey

The results of the GRSR questionnaire varied between groups. The reflux score of the patients with RE and DES was higher

**Table 2**  
**The results of esophageal manometry.**

	RE (n=35)	HE (n=63)	FH (n=104)	NERD (n=94)
HH, n, %	25, 71.43	0	0	31, 32.98
Absent peristalsis, n, %	8, 32.00	0	0	0
Weak peristalsis, n, %	9, 25.71	0	0	3, 3.19
Failed swallows, %*	47.71 ± 28.40	15.56 ± 9.63	13.27 ± 9.90	18.94 ± 12.31
LES length	3.01 ± 0.60	3.07 ± 0.59	3.09 ± 0.39	3.06 ± 0.57
Basal LES pressure, mm Hg*	7.47 ± 3.00	17.51 ± 2.93	17.18 ± 2.76	9.98 ± 5.59
LESPI, mm Hg/s/cm*	194.57 ± 11.71	372.67 ± 45.80	371.22 ± 44.70	253.88 ± 86.65
CFV, cm/s	3.13 ± 0.66	3.06 ± 0.65	3.11 ± 0.62	3.27 ± 1.03
DCI, mm Hg/cm/s*	580.06 ± 500.13	2086.63 ± 1023.35	1940.11 ± 823.95	923.97 ± 291.82
Basal UES pressure, mm Hg*	82.74 ± 15.64	115.24 ± 77.25	123.12 ± 92.25	80.06 ± 15.07

CFV = contractile front velocity, DCI = distal contractile integral, FH = functional heartburn, HE = hypersensitive esophagus, HH = hiatal hernia, LES = lower esophageal sphincter, LESPI = esophageal sphincter pressure integral, NERD = nonerosive gastroesophageal reflux disease, RE = reflux esophagitis, UES = upper esophageal sphincter.

\* Means  $P < 0.05$  between varied groups.

**Table 3****24-Hour impedance-pH monitoring.**

	RE (n = 35)	HE (n = 63)	FH (n = 104)	NERD (n = 94)
Impedance parameters				
Acid				
Upright*	38.03 ± 13.65	3.94 ± 2.03	3.94 ± 1.83	12.47 ± 5.08
Recumbent*	11.83 ± 4.76	4.14 ± 2.66	3.95 ± 2.08	3.78 ± 2.09
After meal*	33.51 ± 10.57	23.43 ± 6.52	23.37 ± 6.39	23.35 ± 6.54
Weakly acid				
Upright*	3.63 ± 2.09	12.89 ± 5.02	12.44 ± 4.86	12.74 ± 4.86
Recumbent*	3.69 ± 2.18	12.21 ± 4.81	11.79 ± 4.54	11.49 ± 4.18
After meal*	3.69 ± 2.04	12.23 ± 4.75	12.23 ± 4.78	11.82 ± 4.66
Nonacid				
Upright	0.77 ± 0.69	0.81 ± 0.67	0.83 ± 0.67	0.80 ± 0.67
Recumbent	0.77 ± 0.69	0.79 ± 0.68	0.79 ± 0.67	0.79 ± 0.67
After meal	0.86 ± 0.69	0.70 ± 0.66	0.58 ± 0.51	0.59 ± 0.50
Type of reflux				
Liquid*	35.83 ± 11.68	17.75 ± 4.13	17.37 ± 4.13	34.22 ± 6.59
Gas*	22.94 ± 10.57	35.08 ± 7.11	34.56 ± 6.89	16.73 ± 4.32
Mixed*	31.23 ± 6.91	18.62 ± 5.13	17.03 ± 4.32	16.73 ± 4.32
% Bolus exposure				
Upright*	3.63 ± 1.26	0.71 ± 0.68	0.67 ± 0.64	3.67 ± 1.24
Recumbent	0.83 ± 0.66	0.79 ± 0.66	0.79 ± 0.68	0.78 ± 0.69
After meal*	3.69 ± 1.39	1.71 ± 1.11	1.77 ± 1.08	1.71 ± 1.10
pH Parameters				
DeMeester score*	36.53 ± 18.16	5.11 ± 3.15	4.63 ± 3.10	20.24 ± 4.07
% AET				
Upright*	20.64 ± 6.62	13.83 ± 9.18	4.22 ± 2.32	19.92 ± 6.55
Recumbent*	7.65 ± 5.82	1.43 ± 1.10	1.51 ± 1.30	7.31 ± 5.67
After meal*	20.28 ± 5.96	5.61 ± 1.93	5.45 ± 1.93	18.90 ± 5.56

AET = acid exposure time, FH = functional heartburn, HE = hypersensitive esophagus, NERD = nonerosive gastroesophageal reflux disease, RE = reflux esophagitis.

\* Means  $P < 0.05$  between varied groups.

compared to the other patients ( $P < 0.05$ ). The abdominal and diarrhea scores in HE, FH, and NERD groups were higher than in the other groups (all  $P < 0.05$ ), while constipation scores in the HE and FH groups were higher than in the other groups ( $P < 0.05$ ) (Table 4).

#### 4. Discussion

GERD is a chronic condition in which the contents refluxed from the stomach and duodenum cause troublesome symptoms and/or complications. This disease negatively impacts a patient's quality of life, and its investigation and treatment can be costly.<sup>[19]</sup> PPIs have proven to be very efficient at treating GERD. Unfortunately, a large number of patients seen in clinical practice do not respond well to PPI therapy. Ates and Vaezi<sup>[20]</sup> described these patients as

having “refractory symptoms,” thus suggesting that reflux disease may not be the sole cause of these symptoms. Herregods et al<sup>[21]</sup> reported that among 106 patients presenting with persistent typical reflux symptoms, only 69 patients received a final diagnosis of GERD. This finding is consistent with our own, which revealed that among patients with PPI-refractory symptoms, only 37.72% were associated with reflux disease. Therefore, it is important to differentiate between GERD and other related diagnoses in order to provide precise and cost-effective treatments for PPI-refractory patients.

Several academic associations have recommended quality of life/symptomatic questionnaires for the assessment of reflux symptoms given their favorable cost-benefit profile.<sup>[22,23]</sup> We found that the reflux, abdominal, diarrhea, and constipation ratings of the GSRS questionnaire were significantly different

**Table 4****The results of questionnaire survey.**

	RE (n = 35)	HE (n = 63)	FH (n = 104)	NERD (n = 94)	Achalasia (n = 38)	Hypertensive (n = 6)	DES (n = 3)
GERD-HRQL	29.31 ± 4.98	28.75 ± 5.22	29.72 ± 5.12	29.78 ± 5.44	30.71 ± 5.25	34.33 ± 5.89	26.67 ± 1.53
FSSG	16.06 ± 2.41	15.38 ± 2.28	15.21 ± 2.55	15.27 ± 2.81	15.29 ± 2.75	14.33 ± 5.16	14.67 ± 0.58
GSRS							
Reflux*	6.05 ± 0.17	4.67 ± 0.62	4.71 ± 0.63	5.49 ± 0.84	5.50 ± 0.83	4.50 ± 1.05	5.67 ± 0.58
Abdominal*	5.00 ± 1.11	7.18 ± 1.18	7.13 ± 1.22	6.98 ± 1.32	4.66 ± 1.12	4.33 ± 1.21	5.00 ± 1.00
Indigestion	7.17 ± 0.79	7.22 ± 0.78	7.20 ± 0.78	7.18 ± 0.78	7.16 ± 0.79	7.33 ± 0.82	7.00 ± 1.00
Diarrhea*	2.91 ± 0.70	3.87 ± 0.77	4.01 ± 0.77	4.03 ± 0.77	2.50 ± 0.80	2.67 ± 0.82	1.67 ± 0.58
Constipation*	4.23 ± 0.84	6.32 ± 1.20	6.42 ± 1.20	4.85 ± 1.67	4.76 ± 1.13	4.67 ± 1.03	3.00 ± 1.00

DES = diffuse esophageal spasm, FH = functional heartburn, FSSG = frequency scale for the symptoms of gastroesophageal reflux disease, GERD-HRQL = gastroesophageal reflux disease-health-related quality of life, GSRS = Gastrointestinal Symptom Rating Scale, HE = hypersensitive esophagus, NERD = nonerosive gastroesophageal reflux disease, RE = reflux esophagitis.

\* Means  $P < 0.05$  between varied groups.

between our study groups. Our results support the report by Zerbib et al<sup>[24]</sup> which found that functional dyspepsia and irritable bowel syndrome are strongly associated with refractory symptoms in patients with documented abnormal reflux. A systematic review of 9 clinical trials showed that high levels of anxiety at baseline were associated with persistent reflux-like symptoms.<sup>[25]</sup> This highlights the need for more attention to patients' psychological status. The value of questionnaires in patients with refractory GERD symptoms also requires further investigation.

HRM, with its multiple pressure sensors and solid-state sensor technology, has proven to be a sensitive method for assessing esophageal body motility and function.<sup>[26]</sup> In our study, we identified 15.54% of total cases with esophageal motility disorders. Patients with achalasia or other esophageal body motility disorders presently similarly to GERD and thus are often misdiagnosed. Impedance pH monitoring is believed to increase the sensitivity of reflux monitoring to as high as 90%.<sup>[27]</sup> The main advantage of this technique lies in its ability to measure reflux while on PPIs and also monitor nonacid reflux, which occurs commonly in patients on PPI therapy.<sup>[28]</sup> Our data are consistent with Savarino et al<sup>[29]</sup> Acid reflux occurred more frequently in patients with RE than in the other patients. Moreover, we found that HE and FH groups have weakly acidic and gas reflux, while acid and liquid reflux occurs more commonly in the RE and NERD groups. Gas mixed with liquid reflux was predominant in the RE group. The different patterns of reflux among these patients with refractory symptoms are due to unidentified mechanisms that must be elucidated through continued research, especially if this may help clinicians to better control their patients' symptoms.

The percent of bolus exposure time (BET) is defined as the sum of the duration of all reflux episodes (regardless of pH) divided by the time monitored. The BET is considered pathological when >1.4%.<sup>[30]</sup> Some researchers believe that BET is a more suitable indicator for judging distal esophageal reflux, especially in the field of medication research. A recently published report confirmed that PPI therapy not only changed the chemical composition of the reflux contents but also significantly reduced the total number of reflux episodes and the BET.<sup>[31]</sup> In a study of patients with refractory symptoms, Khan et al<sup>[32]</sup> classified patients with NERD based on their BET. Our data showed that RE and NERD patients have a longer BET when upright compared to FH and HE patients.

We first investigated the types of reflux in patients with refractory symptoms. Mixed reflux of gas and liquid was previously thought to occur more frequently than pure liquid reflux in healthy subjects and in patients with GERD.<sup>[33]</sup> Our results showed that liquid reflux occurred more frequently in GERD (RE and NERD) than non-GERD (FH and HE) groups, while gas reflux was more common in the non-GERD group. Mixed reflux was the most frequent in the RE group. Fujiwara et al<sup>[34]</sup> demonstrated that liquid reflux is more common in patients when they are asleep than before falling asleep. Further investigation into the types of reflux will be helpful in helping us to understand the complex mechanism of GERD.

Unfortunately, there were some limitations to our study that should be acknowledged. Due to noncompliance issues, we were not able to recruit a sufficient number of patients currently taking PPIs in order to compare their results to those obtained from patients off PPIs. Furthermore, it would have been advantageous to extend the time of the impedance pH monitoring to more than 24 hours.

In conclusion, the results of our study suggest that it is important to differentiate refractory GERD symptoms from other diseases not related to reflux. HRM, impedance pH monitoring, and GSRS questionnaires are effective, sensitive methods to make this distinction. Finally, we propose that it is also worth investigating the different types of reflux in order to better understand the mechanism of refractory GERD symptoms.

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