Original Article

A Comparison Study of Esophageal Perception to Mechanical and Chemical Stimulation in Patients with Typical Gastroesophageal Reflux Symptom and Atypical Gastroesophageal Reflux Symptom

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ABSTRACT

Background: The symptoms of gastroesophageal reflux disease (GERD) are of two major types. Typical GERD symptoms are mainly heartburns or acid regurgitation while atypical GERD symptoms may involve a variety of organ systems, including respiratory, ENT, and cardiovascular symptoms. The underlying mechanisms for the differing major symptom manifestations remain unknown. This study was aimed to compare esophageal sensitivity to balloon distension and acid infusion between the both major groups. We hypothesized that visceral perception in each group was different.

Material and Method: The diagnosis of GERD was based on an ambulatory pH monitoring for all study patients. Perceptual responses to esophageal balloon distension and intraluminal acid perfusion were evaluated in 9 typical GERD patients and in 7 atypical GERD patients. Mechanosensitivity was evaluated with a barostat using unbiased distension protocols and verbal ratings of sensations (no sensation, moderate sensation, discomfort, and pain). Chemosensitivity to acid was determined by employing the visual analogue scale and the acid perfusion intensity score.

Results: Typical GERD patients showed a higher volume threshold of esophageal discomfort perception in response to phasic distension than atypical GERD patients (26.66 ± 7.91 ml VS. 18.75 ± 4.40 ml, $p < 0.05$). The perception score in response to acid perfusion in both groups was similar.

Conclusion: Atypical GERD patients had lower threshold for esophageal discomfort in response to balloon distension compared to typical GERD cases, whereas the sensation thresholds in response to acid perfusion into the esophagus were not different.

Key words : gastroesophageal reflux disease, GERD, esophageal perception, acid perfusion

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INTRODUCTION

According to the Montreal definition and classification, GERD is a condition which develops when reflux of stomach contents causes troublesome symptoms and/or complications[1]. The prevalence of GERD varies in different parts of the world. In a systemic review by Wong[2], the prevalence of GERD in eastern Asia ranged from 2.5%-6.7% for at least weekly symptoms of heartburn and/or acid regurgitation, the so-called "typical GERD". Heartburn or acid regurgitation had a very high specificity (89% and 95%, respectively) but a low sensitivity (38% and 6%) for typical GERD.[3]

However, a subgroup of patients presents a collection of signs and symptoms that are not directly related to esophageal damage. These are known collectively as the atypical manifestation of gastroesophageal reflux disease (atypical GERD). It has been shown that GERD is associated with pulmonary symptoms, as well as with lower airway diseases(asthma, chronic cough, bronchitis, aspiration pneumonia and idiopathic pulmonary fibrosis), otorhinolaryngologic signs/symptoms (hoarseness, laryngitis, subglottic stenosis, vocal cord granuloma and laryngeal carcinoma) and other atypical manifestations (noncardiac chest pain, dental erosion, sinusitis, pharyngitis, and sleep apnea)[4,5]. Most patients with atypical GERD do not present with typical symptoms. This makes it difficult to diagnose atypical GERD, and the true prevalence of GERD may have been underestimated.[5]

Results from several studies explain the pathogenesis of GERD. Transient relaxation of the lower esophageal sphincter (tLESR) is thought to be the key motility disorder underlying GERD[6]. In addition, abnormal acid clearing through the esophagus and abnormal upper gastrointestinal movement disorder also play a role in the pathogenesis of GERD.

DiBaise *et al*.[7] elucidated the patterns of clinical presentation in typical GERD and atypical GERD. Many parameters of both groups were compared including the percent age of total time with pH <4, the lower esophageal sphincter relaxation pressure, the upper esophageal sphincter relaxation pressure and the distal contraction amplitude. All of these parameters were not statistically different. Trimble *et al*.[8] compared the sensory threshold in response to esophageal distension between subjects with GERD symptoms and GERD patients. The results showed a spectrum of visceral sensitivity in GERD, with enhanced esophageal sensation in those patients with symptomatic but not excessive gastroesophageal reflux, indicating that their symptoms resulted from a heightened perception of normal reflux events. Such conclusion was also confirmed by a study of Rodriguez-Stanley *et al*.[9] which showed that esophageal hypersentivity may play a major role in producing heartburns.

Although many studies have delineated the pathogenesis of GERD, the true mechanisms in typical GERD and atypical GERD with varying symptoms are not known for certain. Our cross-sectional study was designed to demonstrate sensory thresholds to both mechanical stimulation and chemical stimulation, and to compare these findings in typical GERD and atypical GERD cases.

MATERIALS AND METHODS

Study subjects

Nine typical GERD patients (2 males, 7 females; mean age, 51.44 ± 13.13 years) and 7 atypical GERD patients (2 males, 5 females; mean age 45.29 ± 9.78 years) were recruited into the study. All patients were evaluated by a personal interview, 24-hour esophageal pH monitoring, and esophagogastroduodenoscopy (EGD). Inclusion into the study required GERD symptoms to the present for at least 3 months. In cases of typical GERD, patients must have heartburns and/or acid regurgitation at least more than once a week with moderate symptom severity. Atypical GERD patients must also have symptom apart from heartburns and acid regurgitation for at least 3 months. The symptoms of atypical GERD were sore throat, dysphagia, throat clearing, chest pain, and chronic cough. Exclusion criteria were age over 65, history of upper gastrointestinal surgery, peptic ulcer disease, autonomic or peripheral neuropathy, myopathy, uncontrolled diabetic mellitus, functional bowel disorder and ingestion within the preceeding week of any medications that may affect perception of symptoms, lower esophageal sphincter pressure, or acid-clearance mechanism. The study protocol was approved by the Ethics Committee of Chulalongkorn University. All patients gave informed consent to participate.

Study design

GERD symptom questionnaire: All subjects enrolled to the study completed a GERD symptom questionnaire that assessed the occurrence of heartburns,

acid regurgitation, chest pain, dysphagia, sore throat, throat clearing and chronic cough, the influence of GERD symptoms on lifestyle and healthcare use, respiratory complaints and other upper gastrointestinal symptoms, esophageal abnormalities, and history of surgery. All symptoms were rated for the frequency of symptom (none, more than once a day, more than once a week but less than once a day, and less than once a week) and for the severity of symptoms (mild, moderate, and severe).

24-hour esophageal pH monitoring: All subjects underwent esophageal pH monitoring. After an overnight fast, a dual channel pH probe (Medtronic, Mineapolis, MN) was inserted nasally into the stomach. The dual channel pH probe was connected to a digital portable recorder. The probe was placed 5 cm above the manometrically defined proximal margin of the LES. A reference electrode was attached to the upper chest. Subjects were instructed to keep a diary, recording meal times, position changes, and the time and type of their dyspeptic symptoms. They were encouraged to pursue their daily activities and taken their usual diet. At the beginning and at the end of the study, the electrode and the system were calibrated in standard solutions of pH 1 and pH 7. Reflux was defined as pH below 4, and a positive 24-hour esophageal pH monitoring was established when the percent age of total time of pH <4 was >3.75% at the distal channel and was ≥1% at the proximal channel. Analysis of the recorded data was performed by using SPSS version 13.0 software.

Esophageal distention test: The balloon distension protocol was adapted from Fass R[10]. A computer-driven volume-displacement device (electronic barostat) was used to inflate and deflate the balloon under two protocols. Firstly, ramp phase, using a barostat to continuously stepwise inflate a balloon, and keep in plateau volume for 30 seconds in each step, starting at 10 mL and then 5 mL for each cycle. Subjects were then advised to take a rest for 5 minutes. Lastly, phasic distension phase, employing a barostat to inflate a balloon, to keep in plateau volume for 45 seconds, and deflate volume from a balloon. Its volume started in stepwise pattern, 10, 15, 20,..., 110 mL. The maximum volume in both protocols was 110 mL. Subjects were instructed to report sensory perception in 4 levels: no sensation, moderate sensation, discomfort, and pain. When a subject reported pain sensation during phasic or ramp distention, the device deflated instantaneously. There was a fixed pressure limit that also triggered balloon deflation for pressures of 60 mm Hg. A latex balloon was attached to a plastic probe (diameter, 10F) and tied at the proximal and the distal ends. The distance between the two attachment sites was 5.0 cm. The balloon was mounted over three ports used for inflation and intraballoon pressure and volume measurements. The balloon was inflated before initial use and after completion of each experiment to ensure that there were no leaks. Patients were placed in the supine position on a bed. The balloon was inserted via the nostril and positioned at 5 cm above the lower esophageal sphincter. The investigator remained in the room throughout the test, and limited his interaction with the subject only to explanation about respective tasks. Patients were not given specific information about the nature of the distention protocols (i.e., ramp distention vs. random phasic distention). During each protocol, subjects were able to terminate the test at any time if they experienced too much discomfort.

Modified acid perfusion test: The acid perfusion test was adapted from Fass R[10]. All patients underwent an acid perfusion test, preceded by esophageal manometry to determine the position of the proximal margin of the LES. A manometry catheter with a central lumen was inserted via the nasal passage and was placed in the mid-esophagus, 10 cm above the upper border of the LES. Saline was infused into the esophagus at a rate of 10 mL/min for 2 minutes. Subsequently, without the patient's knowledge, 0.1N hydrochloric acid was infused for 5 minutes at a similar rate. Patients were instructed to report whenever their heartburn symptoms were reproduced, using visual analogue scale to determine the intensity of symptom. Chemosensitivity was assessed as both the duration of typical symptom perception expressed in seconds and a total sensory intensity rating at each minute of acid perfusion, using a visual analogue scale. The scale consists of a 10-cm horizontal bar flanked by descriptors of increasing intensity. An acid perfusion test intensity score (cm × s) was then calculated as follows:

$$\frac{(I \times T)}{100}$$

where I is the total intensity rating at the end of acid perfusion and T is the duration of typical symptom perception. For convenience the score was divided by 100.

Statistic analysis

Results are expressed as means ± SEM. To determine the difference of esophageal balloon distension perception thresholds (typical GERD vs. atypical GERD), an unpaired-T test was performed. The acid intensity scores were also compared between both groups, using an unpaired-T test. Chi-square tests were calculated to investigate the association among esophageal grading, esophageal manometry abnormalities, and number of patients with chest pain. Level of α was set at $p < 0.05$ throughout.

RESULTS

Patient characteristics

Table 1 summarizes the clinical characteristics of patients with typical GERD and atypical GERD, including sex, age, body mass index (BMI), percent time of esophageal pH <4 and endoscopy finding. Typical GERD patients seemed to be older and have more BMI than atypical GERD patients. However, the data of percentage time of esophageal pH monitoring more than 4 at the upper and the lower probes was nonparametric and showed statistical significant at the upper probe.

Table 2 showed the symptom severity of typical and atypical GERD patients. There were 3 levels of symptom severity (0 = no symptom; 1 = mild symptom, not disturb quality of life; 2 = moderate symptom, disturb quality of life, do not need behavioral change; 3 = severe symptom, disturb quality of life and need behavioral change). Apart from medium severity of heartburns, all data were not statistically significant.

Sensory thresholds in the esophagus during ramp phase distention

During ramp phase distention, mean perception thresholds for moderate sensation in the esophagus were similar between typical GERD patients and atypical GERD patients (18.33 vs. 20.00, p = 0.67). The mean discomfort thresholds in typical GERD patients and atypical GERD patients were 26.88 and 25.71, respectively (p = 0.78). Because of an upper pressure safety limit (60 mmHg), only 3 patients with typical GERD and 4 patients with atypical GERD were analyzed for mean pain threshold. There was no statistical difference in both groups (Table 3).

Sensory thresholds in the esophagus during phasic distention phase

As shown in table 4, the mean thresholds for moderate sensation during phasic distention phase in the esophagus were similar between typical GERD

Table 1 Clinical characteristics of patients with GERD

Parameter	Typical GERD (n = 9)	Atypical GERD (n = 7)	p value
Sex (% female)	77.8	71.4	1.00
Age (year)	51.44 ± 13.13	45.29 ± 9.78	0.32
BMI (Kg/m^2)	23.66 ± 4.80	22.59 ± 4.47	0.65
Percent time of esophageal pH<4 (Median, range)			
- % time at upper channel	2.80 (1-49)	0.70 (0-3)	0.02*
- % time at lower channel	7.50 (1-25)	3.40 (0-13)	0.32*
Resting lower esophageal sphincter (mmHg)	30.96 ± 19.86	19.99 ± 10.42	0.21
Number of patients with esophageal manometry			
- Normal	5	1	0.06
- Abnormal	4	6	
Endoscopy grading**			
- normal	7	4	1.00
- grade A, B	2	3	
- grade C, D	0	0	

*Mann-Whitney U test
**Using the LA classification

Table 2 Symptom severity of patients with typical GERD and atypical GERD

Symptom severity	Typical GERD (n = 9)	Atypical GERD (n = 7)	p-value
Number of patients with heartburn			
no	1	4	0.106
mild	0	1	0.438
moderate	8	1	0.009
severe	0	0	1.00
Number of patients with acid regurgiation			
no	4	4	1.00
mild	2	1	1.00
moderate	3	1	0.583
severe	0	0	1.00
Number of patients with chest pain			
no	1	0	1.00
mild	0	2	0.175
moderate	8	4	0.262
severe	0	0	1.00
Number of patients with chronic cough			
no	7	6	1.00
mild	0	1	0.438
moderate	2	0	0.475
severe	0	0	1.00
Number of patients with sore throat			
no	2	3	0.106
mild	4	3	0.615
moderate	3	1	0.585
severe	0	0	1.00

Table 3 Esophageal balloon distension perception threshold during ramp phase

Sensation	Typical GERD Volume thresholds (mL)	Atypical GERD Volume thresholds (mL)	p value
Moderate sensation	18.33 ± 8.30 (n = 9)	20.00 ± 7.07 (n = 7)	0.67
Discomfort	26.88 ± 8.84 (n = 8)	25.71 ± 6.73 (n = 7)	0.78
Pain	23.33 ± 7.63 (n = 3)	30.00 ± 4.08 (n = 4)	0.19

patients and atypical GERD patients (p = 0.27). Interestingly, the mean discomfort threshold of typical GERD patients (26.67 ± 7.91 mL) was statistically different from the mean discomfort threshold of atypical GERD patients (17.75 ± 4.40 mL). However, the mean pain thresholds of typical GERD patients and atypical GERD patients were not sufficient to show difference between both groups due to small numbers of patients left in both group (2 patients with typical GERD and 5 patients with atypical GERD)

Acid perfusion test

The acid perfusion was not a good provocative test in patients with GERD symptom. In this study, the acid perfusion test was positive in 55% of typical GERD patients and 57.14% of atypical GERD patients. Time to onset of positive acid perfusion test was similar in both groups. The intensity score of both typical GERD patients and atypical GERD patients were shown in table 5. The mean intensity score of typical GERD patients (n = 4) was 8.85 ± 8.87, which the mean

Table 4 Esophageal balloon distension perception threshold during phasic phase

Sensation	Typical GERD Volume thresholds (mL)	Atypical GERD Volume thresholds (mL)	p value
Moderate sensation	19.44 ± 8.82 (n = 9)	15.00 ± 5.77 (n = 7)	0.27
Discomfort	26.67 ± 7.91 (n = 9)	17.75 ± 4.40 (n = 6)	0.045
Pain	22.50 ± 10.61 (n = 2)	26.00 ± 6.52 (n = 5)	0.60

Table 5 The acid perfusion test in patients

	Typical GERD	Atypical GERD	p value
Numbers of patient with positive acid perfusion test	4/9 (44.44%)	4/7 (57.14%)	1.00
Time to onset of positive acid perfusion test	120 ± 60	180 ± 60	0.29
Acid intensity score	8.85 ± 8.87	8.53 ± 5.35	0.60

intensity score of atypical GERD (n = 4) was 8.85 ± 5.35. There was no statistical significance between the two groups.

DISCUSSION

Intraesophageal balloon distension test; we have shown in this study that patients with typical GERD symptom had a higher threshold for esophageal discomfort in response to balloon distension compared to patients with atypical GERD symptom. To explain the difference between the two groups, we initially analyzed their baseline characteristics. All parameters did not show any difference, except the percentage time of esophageal pH monitor below 4. These data were nonparametric using Mann-Whitney U test. There were no previous data that would suggest that the level of acid exposure time could influence the esophageal perception. An abnormal esophageal manometry was considered a possible cause of visceral esophageal hypersensitivity in the past study. There were some studies comparing patients with non-cardiac chest pain and typical GERD patients which suggested that patients with non-cardiac chest pain had a lower threshold than typical GERD patients[11,12]. A number of patients with abnormal esophageal manometry in atypical GERD patients seemed to be higher than typical GERD patients although not statistically significant. These findings indicated that motility disorder may be a cause of symptom presentation. However, a recent study considered visceral hypersensitivity to be the possible cause to explain this difference. There was a study of GERD with visceral perception by Rao *et al*.[13] Who employed atropine in all patients with GERD to diminish esophageal motility disorder that may interfere visceral perception. Interestingly, the results showed that patients with GERD had a lower threshold of visceral compared to normal subjects. It was concluded that visceral hypersensitivity may be the cause of symptom in patient with GERD. Such conclusion was confirmed by Smout *et al*.[14] who showed that visceral hypersensitivity by cerebral evoked potential was lower in non-cardiac chest pain compared to normal subjects. Thus, the explanation from our study was one of visceral hypersensitivity in patients with GERD symptom. Additionally, patients with atypical GERD symptom may have higher visceral hypersensitivity compared to patients with typical GERD symptom. This conclusion has to be confirmed by future study.

There were some limitations in our study because the upper pressure limit of barostat was set at the level of 60 mmHg by the manufacture. Thus, some patients who could have tolerated higher volume, particularly pain threshold, would be lost from pooled of data analysis, owing to because alarming shut down of the barostat. Nevertheless, we tried to analyze the valid data and compare both groups. Interestingly, the discomfort thresholds in extraesophgeal GERD patients were lower than in typical GERD patients.

The other limitation of balloon distension study was neither the standard protocol nor the type of balloon. Each study had their own protocol of distension and their type of balloon. Thus, the results from different studies were not comparable. We tried to mini-

mize the internal errors in our study by using the same protocol for all patients, using the same balloon and employing only one investigator.

To compare the chemosensitization by using acid perfusion test, acid perfusion was performed in both groups. The results in both groups were similar, and also similar to previous study. The acid perfusion test was not accurate enough to diagnose GERD[10,15]. It had either a low sensitivity or a low specificity for diagnosing GERD. We tried to reproduce the heartburn symptom in both groups, but that was reproducible only 44.44% in patients with typical GERD symptom. Interestingly, Fass *et al*.[10] revealed no difference of sensory threshold between normal subjects and patients with GERD symptoms.

Our study has provided more knowledge about the symptoms of GERD. We learned something more about the pathogenesis of the symptom in each group. Visceral hypersensitivity underlies the pathogenesis of patients' symptom, especially patients with atypical GERD and abnormal esophageal manometry. However, further study is needed to find out more in detail of visceral hypersensitivity, and to test visceral perception in patients with other symptoms.

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