



RAPID COMMUNICATION

## Is ineffective esophageal motility associated with gastropharyngeal reflux disease?

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### Abstract

**AIM:** To evaluate the association between ineffective esophageal motility (IEM) and gastropharyngeal reflux disease (GPRD) in patients who underwent ambulatory 24-h dual-probe pH monitoring for the evaluation of supraesophageal symptoms.

**METHODS:** A total of 632 patients who underwent endoscopy, esophageal manometry and ambulatory 24-h dual-pH monitoring due to supraesophageal symptoms (*e.g.* globus, hoarseness, or cough) were enrolled. Of them, we selected the patients who had normal esophageal motility and IEM. The endoscopy and ambulatory pH monitoring findings were compared between the two groups.

**RESULTS:** A total of 264 patients with normal esophageal motility and 195 patients with the diagnosis of IEM were included in this study. There was no difference in the frequency of reflux esophagitis and hiatal hernia between the two groups. All the variables showing gastroesophageal reflux and gastropharyngeal reflux were not different between the two groups. The frequency of GERD and GPRD, as defined by ambulatory pH monitoring, was not different between

the two groups.

**CONCLUSION:** There was no association between IEM and GPRD as well as between IEM and GERD. IEM alone cannot be considered as a definitive marker for reflux disease.

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**Key words:** Ineffective esophageal motility; Gastroesophageal reflux disease; Gastropharyngeal reflux disease

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### INTRODUCTION

Gastroesophageal reflux disease (GERD) is characterized by increased exposure of the esophageal mucosa to the gastric contents. This is mainly due to a various combinations of an increased number of gastroesophageal reflux episodes and abnormally prolonged clearance of the refluxed material<sup>[1,2]</sup>. The mechanisms for efficient clearance are effective peristalsis, the volume of saliva and gravity.

Ineffective esophageal motility (IEM) is the most recently described esophageal motility abnormality. IEM is defined as contractions with an amplitude of less than 30 mmHg and/or with a rate of nontransmission to the distal esophagus in number of 30% or more of water swallows<sup>[3,4]</sup>. IEM is associated with an increased acid clearance times in the distal esophagus<sup>[3]</sup>. Increased acid exposure in these patients is associated with the development of erosive esophagitis and GERD-

associated respiratory symptoms<sup>[5,6]</sup>.

Gastropharyngeal reflux, also called laryngopharyngeal reflux, is a term used to describe esophageal acid reflux into the laryngeal and pharyngeal areas. It causes supraesophageal manifestations (*e.g.* globus, chronic cough, hoarseness, asthma, chronic sinusitis, or other pulmonary or otorhinolaryngologic diseases). Currently, the best way to demonstrate gastropharyngeal reflux is ambulatory 24-h dual probe pH monitoring<sup>[7]</sup>.

It might be hypothesized that patients with IEM would be unable to clear refluxed acid; this would lead to a prolonged esophageal dwell time of the refluxed acid and then the refluxed acid would reach to a higher level. As a result, it would be presumed that patients with IEM have more gastropharyngeal reflux than those patients with normal esophageal motility.

Therefore, the aim of this study was to evaluate the association between IEM and gastropharyngeal reflux in a large series of patients who underwent ambulatory 24-h dual-probe pH monitoring for the evaluation of supraesophageal symptoms.

## MATERIALS AND METHODS

### Study population

We retrospectively analyzed the medical records and the findings from endoscopy, esophageal manometry and ambulatory 24-h pH monitoring of an unselected group of consecutive patients who were referred to our motility laboratory from July, 2003 to December, 2006. A total of 632 patients received all three examinations due to supraesophageal symptoms (*e.g.* globus, hoarseness or cough). Of them, we selected the patients who had normal esophageal motility and a diagnosis of IEM. We did not enroll those patients who had a history of gastric surgery, a diagnosis of scleroderma or those who were on anti-reflux medications at the time of the study.

This study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital.

### Assessment by endoscopy

The presence or absence of reflux esophagitis, hiatal hernia and endoscopically suspected esophageal metaplasia (ESEM) were determined by two endoscopists (G.H. Kim, G.A. Song).

**Reflux esophagitis:** If esophagitis was present, it was graded according to the Los Angeles classification<sup>[8]</sup>.

**Hiatal hernia:** Hiatal hernia was defined as a circular extension of the gastric mucosa above the diaphragmatic hiatus greater than 2 cm in the axial length.

**Endoscopically suspected esophageal metaplasia:** The presence or absence of endoscopically suspected esophageal metaplasia (ESEM) was examined in the lower portion of the esophagus, including the esophagogastric junction, during inflation of the esophagus before inserting the endoscope into the

stomach. The esophagogastric junction was defined as the oral side end of the fold, which exists continuously from the gastric lumen<sup>[9]</sup>, as well as the end of the anal side of the fine longitudinal vessel, because the veins in the lower part of the esophagus were distributed uniformly, running parallel and longitudinally in the lamina propria<sup>[10,11]</sup>. The squamo-columnar junction was defined by a clear change in the color of the mucosa. ESEM was defined as the area between the squamo-columnar junction and the esophagogastric junction.

### Esophageal manometry

All antisecretory and prokinetic medications were discontinued at least 7 d before testing. Esophageal manometry was performed, after an overnight fast, with using an eight-lumen catheter (Synetics Medical Co., Stockholm, Sweden) with side holes 3 cm, 4 cm, 5 cm, 6 cm, 8 cm, 13 cm, 18 cm, and 23 cm from the catheter tip and a water-perfused, low-compliance perfusion system (Synetics Medical Co., Stockholm, Sweden), according to a standard protocol. Briefly, the manometry protocol included the following: First, a station pull-through was performed through the lower esophageal sphincter (LES) to determine the end-expiratory resting pressure, the LES length and the location relative to the nares. The catheter was then positioned with the most distal side-hole 2 cm below the upper margin of the LES. Ten 5-mL water swallows were given to evaluate peristalsis; only the esophageal body contractions, measured at 3 cm, 8 cm and 13 cm above the LES, were recorded for data analysis. The catheter was then pulled through the upper esophageal sphincter (UES) in the same manner (station pull-through) to determine the resting UES pressure, the length and the location relative to the nares. Patients were identified as having IEM when the total sum of the low amplitude peristaltic contractions (the distal amplitude measured at 3 or 8 cm above the LES was < 30 mmHg) and the nontransmitted peristaltic contractions (dropouts at either 3 cm or 8 cm above the LES) was equal or greater than 30% of the total number of swallows used for the esophageal body study<sup>[4]</sup>.

### Ambulatory 24-h dual-probe pH monitoring

Ambulatory 24-h dual-probe pH monitoring was performed immediately after esophageal manometry with using a single-use monocrystalline antimony dual-site pH probe (Zinetics 24, Medtronic Inc., Minneapolis, USA) with the electrodes placed at the tip and 15 cm proximal to the tip. A cutaneous reference electrode placed on the upper chest was also used. All the electrodes were calibrated in buffer solutions of pH 7 initially and then pH 1. The pH catheter was introduced transnasally into the stomach and it was withdrawn back into the esophagus until the electrodes were 5 cm above the proximal margin of the LES. The subjects were encouraged to eat regular meals with restriction for the intake of drink or food with a pH below 4. All the subjects recorded their meal times (start and end), body position (supine and upright) and any symptoms

in a diary. The data were collected using a portable data logger (Ditrigger Mark III, Synetics Medical Co., Stockholm, Sweden) with a sampling rate of 4 seconds, and the data was then transferred to a computer for analysis using "Polygram for Windows" (Release 2.04, Synetics Medical Co., Stockholm, Sweden). For both sites, a decrease in pH below 4, which was not induced by eating or drinking, was considered the beginning of a reflux episode, and the following rise to pH above 4 was considered the end of such an episode. To be accepted as a gastropharyngeal reflux event, the decrease at the proximal probe had to be abrupt and simultaneous with the decrease at the distal probe, or it was preceded by a decrease in pH of a similar or larger magnitude at the distal probe. Thus, acid episodes induced by oral intake, aero-digestive tract residue and secretions, proximal probe movement or loss of mucosal contact in which the proximal pH decline may precede the esophageal pH drop were not included as gastropharyngeal reflux episodes.

The variables assessed for gastroesophageal reflux at the distal probe were the total percentage of time the pH was < 4, the percentage of time the pH was < 4 in the supine and upright positions, the number of episodes the pH was < 4, the number of episodes the pH was < 4 for  $\geq 5$  min, the duration of the longest episode the pH was < 4 and the DeMeester composite score<sup>[12]</sup>.

The variables assessed for gastropharyngeal reflux at the proximal probe were the total percentage of time the pH was < 4, the percentage of time the pH was < 4 in the supine and upright positions, and the number of episodes the pH was < 4.

For the diagnosis of GERD at the distal probe, two different aspects were analyzed<sup>[13,14]</sup>: (1) the total reflux time: the total proportion of the recorded time with pH < 4; a value of > 4% was considered abnormal; (2) the number of reflux episodes: the total number of pH episodes with pH < 4 during the recording; a value of > 35 episodes was considered abnormal.

For the diagnosis of gastropharyngeal reflux disease (GPRD) at the proximal probe, we considered more than 0.1% for the total time, 0.2% for the upright time and 0% for the supine time of pH < 4 to be pathological. For the number of reflux episodes, more than 4 reflux episodes were considered pathological<sup>[15,16]</sup>.

### Statistical analysis

The data are expressed as mean  $\pm$  SE unless otherwise noted. The student *t*-test was used to assess the statistical significance of age, the body mass index, the pressure and length of the LES and the parameters of ambulatory pH monitoring between the two groups. The differences in gender, alcohol intake, smoking, typical reflux symptoms, indications for pH monitoring, reflux esophagitis, hiatal hernia, ESEM, GERD and GPRD, as defined by the ambulatory pH monitoring between the two groups were assessed using the  $\chi^2$  test. A *P* < 0.05 was considered statistically significant. Statistical calculations were performed using the SPSS version 12.0 for Windows software (SPSS Inc., Chicago, IL, USA).

**Table 1** Patient profiles and the endoscopic findings in the patients with normal esophageal motility and ineffective esophageal motility *n* (%)

	Normal ( <i>n</i> = 264)	IEM ( <i>n</i> = 195)	<i>P</i> value
Age (yr, mean $\pm$ SD)	50.8 $\pm$ 11.1	51.1 $\pm$ 12.0	0.782
Gender (men/women)	99/165	87/108	0.125
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	23.6 $\pm$ 2.7	23.2 $\pm$ 2.7	0.393
Alcohol intake	58 (22.0)	31 (15.9)	0.104
Smoking	43 (16.3)	19 (9.7)	0.043
Heartburn/acid regurgitation <sup>1</sup>	128 (48.5)	104 (53.3)	0.304
Indication for pH monitoring			0.542
Globus	118 (44.7)	88 (45.1)	
Hoarseness	63 (23.9)	35 (17.9)	
Cough	27 (10.2)	24 (12.3)	
Sore throat	30 (11.4)	28 (14.4)	
Others <sup>2</sup>	26 (9.8)	20 (10.3)	
Reflux esophagitis <sup>3</sup>	30 (11.4)	30 (15.4)	0.206
A	22	16	
B	7	11	
C	1	2	
D	0	1	
Hiatal hernia	17 (6.4)	10 (5.1)	0.555
Endoscopically suspected esophageal metaplasia	23 (8.7)	11 (5.6)	0.214

<sup>1</sup>More than 2 d per wk; <sup>2</sup>Other indications were halitosis, throat clearing and laryngeal pathology such as vocal polyp; <sup>3</sup>Los Angeles classification grade. IEM: Ineffective esophageal motility.

## RESULTS

A total of 264 patients with normal esophageal motility and 195 patients with the diagnosis of IEM were included in this study. Age, gender, the body mass index, typical reflux symptoms and indications for pH monitoring were not different between the two groups. There was no difference in the frequency of reflux esophagitis and hiatal hernia between the two groups (Table 1).

The LES pressure was lower in the patients with IEM than in those patients with normal esophageal motility. All the variables showing gastroesophageal reflux at the distal probe were not different between the two groups. There was no difference in all the variables showing gastropharyngeal reflux at the proximal probe between the two groups (Table 2).

The frequency of GERD and GPRD, as defined by ambulatory pH monitoring was not different between the two groups (Table 3, Figure 1).

## DISCUSSION

Esophageal acid clearance consists of two processes, first is rapid removal of most of the intraluminal refluxate, which is achieved by gravity and primary or secondary peristalsis (volume clearance), and this is followed by a slow neutralization of the acidified mucosa by the swallowed saliva (chemical clearance). Previous analysis of the relationship between peristaltic dysfunction and the efficacy of esophageal emptying, with using concurrent manometry and fluoroscopy, illustrated that absent or incomplete peristaltic contractions invariably

**Table 2** Results of the lower esophageal sphincter and ambulatory 24-h dual probe pH monitoring in the patients with normal esophageal motility and ineffective esophageal motility

	Normal ( <i>n</i> = 264)	IEM ( <i>n</i> = 195)	<i>P</i> value
Lower esophageal sphincter			
Pressure	21.4 ± 0.5	18.6 ± 0.5	< 0.001
Length	3.3 ± 0.1	3.3 ± 0.1	0.921
Proximal probe			
Time pH < 4 (total) (%)	0.4 ± 0.1	0.7 ± 0.2	0.225
Time pH < 4 (upright) (%)	0.7 ± 0.1	1.0 ± 0.2	0.230
Time pH < 4 (supine) (%)	0.1 ± 0.0	0.6 ± 0.4	0.214
No. of reflux episodes	8.7 ± 1.0	12.2 ± 2.6	0.219
Distal probe			
Time pH < 4 (total) (%)	2.9 ± 0.2	3.5 ± 0.3	0.185
Time pH < 4 (upright) (%)	4.8 ± 0.7	5.0 ± 0.5	0.827
Time pH < 4 (supine) (%)	1.6 ± 0.3	1.9 ± 0.4	0.564
No. of reflux episodes	44.1 ± 2.5	47.8 ± 4.0	0.430
No. of reflux episodes ≥ 5 min	1.4 ± 0.2	1.9 ± 0.3	0.116
Longest reflux episode (min)	8.6 ± 0.8	10.2 ± 1.0	0.199
DeMeester composite score	12.1 ± 0.9	14.1 ± 1.3	0.217

IEM: Ineffective esophageal motility.

**Table 3** Distribution of the patients with gastroesophageal reflux disease and/or gastropharyngeal reflux disease, as defined by ambulatory pH monitoring, in the patients with normal esophageal motility and ineffective esophageal motility *n* (%)

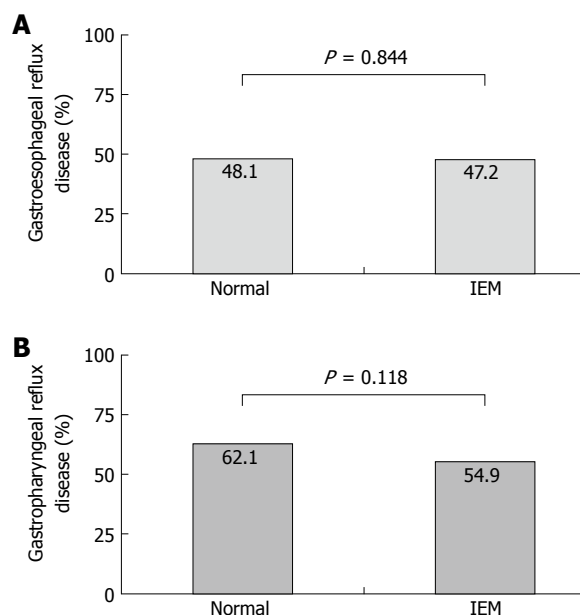
	Normal ( <i>n</i> = 264)	IEM ( <i>n</i> = 195)
GERD and GPRD	108 (40.9)	74 (37.9)
GPRD only	56 (21.2)	33 (16.9)
GERD only	19 (7.2)	18 (9.2)
Normal	81 (30.7)	70 (35.9)

GERD: Gastroesophageal reflux disease; GPRD: Gastropharyngeal reflux disease; IEM: Ineffective esophageal motility.

resulted in little or no volume clearance and ineffective esophageal propulsion of a bolus occurs when the amplitude of the peristaltic waves is below 30 mmHg<sup>[17]</sup>. Thus, peristaltic dysfunction could potentially prolong esophageal acid clearance by delaying the first phase, that of esophageal emptying.

GERD motility abnormalities are part of the nonspecific motor disorders that have been described many years ago<sup>[18]</sup>, and IEM has been found in 20%-50% of the patients with GERD<sup>[19]</sup>. In addition, there have been some studies suggesting a link between IEM and delayed esophageal acid clearance<sup>[3,5,20]</sup>. When GERD patients underwent pH monitoring, there were significantly more recumbent and upright reflux episodes and delayed acid clearance in the patients with IEM than in those patients without IEM<sup>[3,20]</sup>. A greater frequency of IEM was found in patients with respiratory presentations of GERD (chronic cough, asthma and laryngitis) and identification of IEM was particularly useful for patients with supraesophageal GERD<sup>[5]</sup>.

In present study, we selected the patients who had normal esophageal motility and IEM among the patients who received the endoscopy, esophageal manometry and ambulatory pH monitoring due to supraesophageal symptoms. We then analyzed the

**Figure 1** Frequency of gastroesophageal reflux disease (A) and gastropharyngeal reflux disease (B), as defined by ambulatory pH monitoring, in the patients with normal esophageal motility and ineffective esophageal motility (IEM).

degree of gastroesophageal and gastropharyngeal reflux in both group. Our results indicated that IEM was not associated with GPRD as well as GERD, as defined by ambulatory pH monitoring. In addition, all the variables for gastropharyngeal reflux and gastroesophageal reflux were not higher in the patients with IEM than those with normal esophageal motility. These findings are consistent with the previous studies<sup>[21,22]</sup> showing that there was no association between esophageal dysmotility and abnormal acid reflux in patients with supraesophageal GERD symptoms. We also examined the degree of gastroesophageal and gastropharyngeal reflux according to the severity of IEM, but there was no association (data not shown), which was similar to the previous report<sup>[23]</sup> showing that the severity of IEM was not different in erosive and in nonerosive GERD patients. These results suggest that IEM alone is unlikely to be the major determinant of abnormal esophageal acid exposure.

Although many studies have assessed the link between IEM and esophagitis, this issue remains controversial. Most of the previous studies restricted the enrolled subjects to the GERD patients. IEM was associated with reflux esophagitis in some studies of patients with confirmed GERD<sup>[6,24]</sup>. However, other studies showed that the presence of reflux esophagitis was similar between the patients with IEM and those patients with normal esophageal peristalsis<sup>[20]</sup> and there was no difference in the severity of IEM when comparing the erosive and non-erosive GERD patients<sup>[23]</sup>. In our present study, we included the patients who had normal esophageal motility and IEM over a defined period, providing that the ambulatory study had been done in the absence of anti-secretory therapy, thereby insuring the presence of a control group with normal esophageal acid exposure. Our result showed that reflux esophagitis was not associated with IEM.

There were some merits of this study when



comparing it with the previous studies. First, in contrast to previous reports<sup>[5,21,22]</sup> that focused on an association between IEM and supraesophageal reflux disease, our study limited the enrolled subjects to patients with normal esophageal motility and those with IEM to maximize the effect of IEM on GPRD. Second, in the current analysis, we defined GERD and GPRD according to the strict criteria of ambulatory 24-h dual-probe pH monitoring, which is the best available test for diagnosing GPRD, as well as GERD<sup>[7]</sup>. Third, because all the patients in the current study underwent upper endoscopy, we were able to classify them according to the presence or absence of esophagitis and hiatal hernia.

There were some limitations in this study. First, the ambulatory pH monitoring is not 100% accurate and it has a sensitivity as low as 70% in patients with esophagitis, and the sensitivity is substantially lower in patients with nonerosive disease<sup>[25]</sup>, so that some of our patients may have been misclassified. Yet, we included a large number of cases (459 cases), so this limitation was probably lessened. Second, a great deal of controversy exists about the location of the proximal probe. Recording the pH in the hypopharynx is technically difficult. Acid exposure in the hypopharynx can easily be missed because of the relatively large space within the hypopharynx<sup>[15]</sup>. On the contrary, placement of the proximal probe in or below the upper esophageal sphincter allows for more permanent contact with the mucosa during the 24-h period and this results in fewer artifacts<sup>[15,16]</sup>. We used a dual-site pH probe with electrodes placed at the tip and 15 cm proximal to the tip, and we could not choose the exact location of the proximal probe. Yet in most cases (75.4%, 346/459), the proximal probe was located in the UES. So, for the diagnosis of GPRD, we used the criteria proposed by Smit *et al*<sup>[15,16]</sup>.

Why is IEM not associated with GPRD as well as GERD? Conventional manometry may be unable to evaluate the “true effectiveness” of esophageal peristalsis<sup>[26,27]</sup>. In addition, the refluxed acid is neutralized by both the esophageal submucosal secretions and the swallowed salivary secretions, so it becomes non-acid reflux material. Therefore, even though this non-acid refluxate in the upper level actually increased in the patients with IEM, the proximal pH probe cannot detect it. To solve this problem, a prospective study using a combined multichannel intraluminal impedance and pH measurement, which are able to detect both acid and non-acid reflux, as well as the proximal extent of the refluxate, will be needed.

In conclusion, by analyzing a large cohort of patients who had normal esophageal motility and IEM, we demonstrated that there was no correlation between IEM and GPRD, as well as between IEM and GERD, as defined by ambulatory pH monitoring. Although we do not completely exclude that such an association may be possible, IEM alone cannot be considered a definitive marker for reflux (gastroesophageal or gastropharyngeal).

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## COMMENTS

### Background

Ineffective esophageal motility (IEM) is associated with an increased acid clearance times in the distal esophagus. Gastropharyngeal reflux causes supraesophageal manifestations such as globus, chronic cough, hoarseness, asthma, chronic sinusitis, or other otorhinolaryngologic diseases. It might be hypothesized that patients with IEM would be unable to clear refluxed acid; this would lead to a prolonged esophageal dwell time of the refluxed acid and then the refluxed acid would reach to a higher level. As a result, it would be presumed that patients with IEM have more gastropharyngeal reflux than those patients with normal esophageal motility.

### Research frontiers

The research front in this area is focused on evaluating the association of IEM and gastropharyngeal reflux disease (GPRD), as well as gastroesophageal reflux disease (GERD). Although many studies have assessed the link between IEM and esophagitis, this issue remains controversial. Most of the previous studies restricted the enrolled subjects to GERD patients. IEM was associated with reflux esophagitis in some studies of patients with confirmed GERD. However, other studies showed that the presence of reflux esophagitis was similar between the patients with IEM and those patients with normal esophageal peristalsis. This study showed no association between IEM and GPRD, as well as between IEM and GERD in a large series of patients who underwent ambulatory 24-hour dual-probe pH monitoring, for the evaluation of supraesophageal symptoms.

### Innovations and breakthroughs

There are few reports on the association between IEM and GPRD. Most previous studies are symptom-based and lack objective tests such as ambulatory 24-h dual-probe pH monitoring. This study is the largest study to evaluate the association of IEM and GPRD in patients who underwent ambulatory 24-h dual-probe pH monitoring for the evaluation of supraesophageal symptoms.

### Applications

IEM is not associated with GPRD, as well as GERD. Further studies using a combined multichannel intraluminal impedance and pH measurement, which are able to detect both acid and non-acid reflux, as well as the proximal extent of the refluxate, will be needed.

### Terminology

Ineffective esophageal motility (IEM) is defined as contractions with an amplitude of less than 30 mmHg and/or with a rate of nontransmission to the distal esophagus in number of 30% or more of water swallows. Esophageal acid reflux into the laryngeal and pharyngeal areas causes extraesophageal manifestations such as chronic cough, hoarseness, asthma, globus sensation, chronic sinusitis, or other otorhinolaryngologic diseases. This condition is called as gastropharyngeal reflux disease (GPRD).

### Peer review

This is an interesting study since physicians who perform esophageal manometry frequently find IEM. This study is well structured and definitions of esophagitis, GERD and GPRD are adequate since they were based on endoscopy and 24-h dual esophageal pH monitoring.

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