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-probe 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

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[1,2]. 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[3,4]. IEM is associated with an increased acid clearance times in the distal esophagus[5]. Increased acid exposure in these patients is associated with the development of erosive esophagitis and GERD-
associated respiratory symptoms\textsuperscript{(5,6)}. Gastroesophageal reflux, also called laryngopharyngeal reflux, is a term used to describe esophageal acid reflux into the laryngeal and pharyngeal areas. It causes supraesophageal manifestations (\textit{e.g.} globus, chronic cough, hoarseness, asthma, chronic sinusitis, or other pulmonary or otorhinolaryngologic diseases). Currently, the best way to demonstrate gastroesophageal reflux is ambulatory 24-h dual probe pH monitoring\textsuperscript{(9)}.

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 gastroesophageal reflux than those patients with normal esophageal motility.

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

\textbf{MATERIALS AND METHODS}

\textbf{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 (\textit{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.

\textbf{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).

\textbf{Reflux esophagitis:} If esophagitis was present, it was graded according to the Los Angeles classification\textsuperscript{(10)}.

\textbf{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.

\textbf{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\textsuperscript{(11)}, 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\textsuperscript{(10,11)}. 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.

\textbf{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\textsuperscript{(10)}.

\textbf{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 (Digitrapper 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 ≥ 5 min, the duration of the longest episode the pH was < 4 and the DeMeester composite score.[12]

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[13,14]: (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.[15,16]

### Statistical analysis

The data are expressed as mean ± 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 χ² 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).

### 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 (Table1).

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
results in little or no volume clearance and ineffective esophageal propulsion of a bolus occurs when the amplitude of the peristaltic waves is below 30 mm Hg. 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, and IEM has been found in 20%-50% of the patients with GERD. In addition, there have been some studies suggesting a link between IEM and delayed esophageal acid clearance. 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. 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.

In the 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 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 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 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. However, other studies showed that the presence of reflux esophagitis was similar between the patients with IEM and those patients with normal esophageal peristalsis and there was no difference in the severity of IEM when comparing the erosive and nonerosive GERD patients. 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 compared to the previous studies. First, the patients with normal esophageal motility were included. Second, the patients with normal esophageal motility and IEM were selected in the present study. Third, the present study provided a comparison of reflux episodes and acid clearance between the patients with IEM and normal esophageal motility.
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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