

Ineffective esophageal motility and gastroesophageal reflux disease: A close relationship?

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Background/aims: An association between ineffective esophageal motility and gastroesophageal reflux disease is already known, but there are also some conflicting data. We evaluated the association between ineffective esophageal motility and gastroesophageal reflux disease in patients who underwent ambulatory pH monitoring for the evaluation of reflux symptoms at Gazi University, Gastroenterology Clinic. **Materials and Methods:** A total of 239 patients who underwent endoscopy, esophageal manometry and ambulatory 24-h pH monitoring due to reflux symptoms were enrolled. Of them, we selected patients who had normal esophageal motility and ineffective esophageal motility. The endoscopy and ambulatory pH monitoring findings were compared between the two groups. **Results:** Of the 239 patients who presented with reflux symptoms, pathologic acid reflux or endoscopic esophagitis was found in 114 (48%). Ineffective esophageal motility was found in 18 (16%) in the pathologic reflux group and in 4 (3%) in the functional reflux group ($p=0.01$). Ambulatory pH, manometric and demographic findings were compared in ineffective esophageal motility and normal motility groups. Lower esophageal sphincter (LES) pressures were lower in the ineffective esophageal motility group (19.7 versus 16.2; $p=0.01$), and total reflux times in both supine and upright position were higher (10.3 versus 4.9; $p=0.01$) in the ineffective esophageal motility group. Ineffective esophageal motility patients were older and more obese than normal motility group patients. **Conclusions:** This study points to a clear association between ineffective esophageal motility and gastroesophageal reflux disease as defined by ambulatory pH monitoring.

Key words: Ineffective esophageal motility, gastroesophageal reflux disease, motility

İnefektif özofageal motilite ve gastroözofageal reflü hastalığı gerçekten ilişkili mi?

Giriş ve Amaç: İnefektif özofageal motilite ile gastroözofageal reflü hastalığı arasındaki ilişki daha önceki bazı çalışmalarda gösterilmiştir, ancak halen bazı karşıt görüşler de mevcuttur. Biz Gazi Üniversitesi Gastroenteroloji Kliniğine reflü semptomları ile başvuran 24 saatlik pH incelemesi ve özofageal manometrik inceleme yapılan hastalardaki inefektif özofageal motilite ve gastroözofageal reflü hastalığı ilişkisini araştırdık. **Gereç ve Yöntem:** Reflü semptomları ile başvuran özofageal manometri ve 24 saatlik pH incelemesi yapılmış olan 239 hastanın verileri retrospektif olarak incelendi. Bu hastalardan 24 saatlik pH incelemesinde patolojik reflü saptananlarla saptanmayanlar motilite bozuklukları yönünden karşılaştırıldı. Ayrıca tüm grupta normal motilitesi olanlar ile inefektif özofageal motilitesi olan olgular demografik özellikleri, reflü şiddeti yönünden karşılaştırıldı. **Bulgular:** Reflü semptomları ile başvuran 239 hastanın değerlendirmesinde 114 (%48) hastada patolojik asit reflüsü saptandı. Bu grupta inefektif özofageal motilite sıklığı 18 (%16) iken, asit reflüsü saptanmayan grupta 4 (%3) bulundu ($p=0.01$). Patolojik reflüsü olan grupta en sık görülen motilite bozukluğu inefektif özofageal motilite iken ikinci sıklıkta hipotansif alt özofageal sfinkter gelmekteydi. İnefektif özofageal motiliteli hastalar ayrıca incelendiğinde total reflü süreleri hem yatarken hem ayakta yapılan ölçümlerde anlamlı olarak normal motiliteli gruba göre daha yüksekti. Alt özofageal sfinkter basıncı inefektif özofageal motiliteli hasta grubunda daha düşük saptandı (19.7'ye karşı 16.2 $p=0.01$). İnefektif özofageal motiliteli hasta grubunun daha yaşlı ve daha obez olduğu tespit edildi. **Sonuç:** Biz çalışmamızda patolojik asit reflüsü olan hasta grubunda en sık görülen özofageal motilite bozukluğunun inefektif özofageal motilite olduğunu tespit ettik. İnefektif özofageal motilitesi olan hastalarda da daha ciddi asit reflüsü olduğunu saptadık. Bizim çalışmamız inefektif özofageal motilite ile gastroözofageal reflü hastalığı arasında açık bir ilişki olduğunu göstermektedir.

Anahtar kelimeler: İnefektif özofageal motilite, gastroözofageal reflü hastalığı, motilite

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as troublesome symptoms or mucosal damage produced by the abnormal reflux of gastric contents to the esophagus (1). GERD is the third most common gastrointestinal (GI) disorder in adults (2). Major determinants of GERD are acidic content of the refluxate and transient relaxations of the lower esophageal sphincter (LES). Effective esophageal clearance is maintained by esophageal peristalsis, saliva and gravity. Reduced basal LES pressure may facilitate the occurrence of GER episodes, and impaired esophageal body peristalsis may contribute to impaired esophageal clearance (3).

The motility abnormalities associated with GERD were formerly considered as nonspecific esophageal motility disorder (NEMD). However, in recent studies, the definition of ineffective esophageal motility (IEM) has been used more widely and was found to be more accurate. IEM was defined by the presence of distal esophageal peristaltic waves with amplitude lower than 30 mmHg and/or non-transmitted proximal contractions in 30% or more of wet swallows (4). IEM has been found the most common motility disorder in GERD. Patients with GERD have more supine and upright acid reflux and delayed esophageal clearance compared with patients without IEM (5). Whether IEM is a primary esophageal motility disorder or the abnormality is secondary to acid-induced pathologic injury to the esophagus remains controversial (6).

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 reduced LES pressure. It is also known that GERD has been reported to be highly prevalent in obese subjects (7). Therefore, the aims of this study were to evaluate the association between IEM and GERD in a large series of patients who underwent ambulatory 24-hour (h) dual-probe pH monitoring for the evaluation of reflux symptoms and the impact of body weight on esophageal acid exposure and motility.

MATERIALS AND METHODS

Subjects

We retrospectively analyzed the medical records and the findings of esophageal manometry and ambulatory 24-h pH monitoring of patients with GERD symptoms (n=245) in the Department of

Gastroenterology, Gazi University Hospital. Exclusion criteria included previous esophageal or gastric surgery and incomplete examination of the pH-metry or manometric analysis (n=6).

The relationship between esophageal motility and acid exposure was investigated in 239 patients (123 males; mean age 44 years [range: 14-77]).

All 239 patients with typical GERD symptoms were classified into two groups:

Group A: Patients with pathologic pH-metry results (n=114)

Group B: Patients with normal pH metry results (n=125)

Another analysis was done according to manometric studies. Comparison of pH-metry results of patients with normal motility and IEM was also performed.

Esophageal Manometry

Esophageal manometry was performed after an overnight fast 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. All medications known to affect esophageal motility were stopped 24 h before the study. Initially, intragastric pressure was recorded, followed by evaluation of the LES, using station pull-through technique. LES pressure was measured immediately distal to the pressure inversion point, at midexpiratory level. The catheter was then positioned with the most distal side-hole 2 cm below the upper margin of the LES. Ten wet swallows were administered with saline liquid, with a 30-second (s) interval. The esophageal body contractions were measured at 3 cm, 8 cm and 13 cm above the LES. Manometric recordings were generated and stored using a computer software package (Software GERDcheck, Sandhill Scientific Inc., Highlands Ranch, CO, USA).

Definitions of Esophageal Motility Disorders

Normal esophageal motility was defined as having no more than 20% ineffective swallows, with no more than 10% simultaneous swallows, with distal esophageal amplitude <180 mmHg, normal LES basal tone (10-45 mmHg), and normal residual pressure (<8 mmHg). IEM was defined as having distal esophageal pressure <30 mmHg or nontransmitted contractions in $\geq 30\%$ of 10 wet

swallows. Diffuse esophageal spasm was defined as having 20% or more simultaneous contractions. Nutcracker esophagus was defined as normal peristalsis of the esophageal body with average esophageal pressure >180 mmHg. Achalasia was defined as absent esophageal body peristalsis with or without hypertensive LES. Hypotensive LES was defined as having basal tone <10 mmHg. Hypertensive LES was defined as having basal LES tone >45 mmHg (8).

Ambulatory pH Monitoring

All studies were performed with ambulatory pH recording equipment consisting of a portable pH data recorder (Digitrapper, Sandhill) that was connected to a catheter with a single antimony sensor. An external reference electrode was attached to the patient's chest.

After calibration in pH 4.0 and 7.0 solutions, the sensor was positioned 5 cm above the upper edge of the LES, which was determined manometrically as described above. The probe was connected to a data logger (Digitrapper Mark II, Synectics, Sweden), which sampled pH at 5-s intervals for approximately 24 h. Mealtimes, symptom events, and supine periods were recorded in a patient diary. All studies were performed 'off proton pump inhibitor [PPI]' therapy and patients stopped their antisecretory treatment at least seven days before the examination.

On the following day, the equipment was removed and the data downloaded and analyzed (Software GERDcheck, Sandhill).

The variables assessed for GER at the distal probe were the total percentage of time pH was <4, the percentage of time pH was <4 in the supine and upright positions, the number of episodes pH was <4, the number of episodes pH was <4 for ≥ 5 min, the duration of the longest episode pH was <4, and the DeMeester composite score (9). A score above 14.7 (DeMeester score) was considered abnormal. Patients were considered to have abnormal esophageal acid exposure if the fraction time with pH <4 was $\geq 4\%$. This was calculated for both upright and supine positions (9).

Esophagogastrosocopy

Upper endoscopy was performed after an 8-h fast, using a video-endoscope (Olympus GIF-130, Tokyo, Japan). The presence or absence of reflux esophagitis and hiatal hernia was determined by two endoscopists (ME, ID). Reflux esophagitis was

graded according to the Los Angeles classification (10). Hiatal hernia was defined as a circular extension Z-line above the diaphragmatic hiatus greater than 2 cm in the axial length.

Endoscopy was performed as part of the GERD symptoms routine investigation in 152/239 patients. Hiatal hernia was diagnosed endoscopically [Z-line at least 20 mm above the diaphragmatic pinch (11,12)] in 39/150 patients.

Statistical Analysis

Data are expressed as mean values ± 2 SE for each parameter measured. Statistical comparisons were performed using the Mann-Whitney U test for nonnormally distributed data and Student's t test and ANOVA for normally distributed data (with unpaired analysis for intergroup comparison). The data were analyzed using the Statistical Package for the Social Sciences (SPSS) program. All p values were two-tailed with statistical significance indicated by a p value of <0.05.

RESULTS

Table 1 describes the demographic data of 245 patients with typical reflux symptoms. There was male predominance in the normal pH group and pathologic reflux patients had higher body mass index (BMI) levels ($p < 0.05$).

Comparison of Pathologic Reflux and Normal pH-Metry Groups

Figure 1 summarizes the enrollment and distribution of study patients according to pH-metry findings and motility abnormalities. Of the 245 patients, 114 had pathological acid reflux according to the pH-metry results. In the pathologic reflux group, IEM was found in 18 (16%) patients and hypotensive LES in 14 (12%) patients. Normal motility ($n=71$), achalasia ($n=1$), nutcracker esophagus ($n=5$), hypertensive LES ($n=2$), and nonspecific esophageal motility ($n=3$) were also diagnosed.

In the normal pH group, IEM was found in 4 (3%) and hypotensive LES was also found in 4 (3%) patients. Normal esophageal motility ($n=95$), nut-

Table 1. Patients' characteristics in the total group

	Pathologic reflux Number (%) or $\pm$ SD	Normal pH Number (%) or $\pm$ SD
Age	47 $\pm$ 13	42 $\pm$ 12
Female	54 (47%)	69 (55%)
Body mass index	27 $\pm$ 3.5	24.8 $\pm$ 3.5

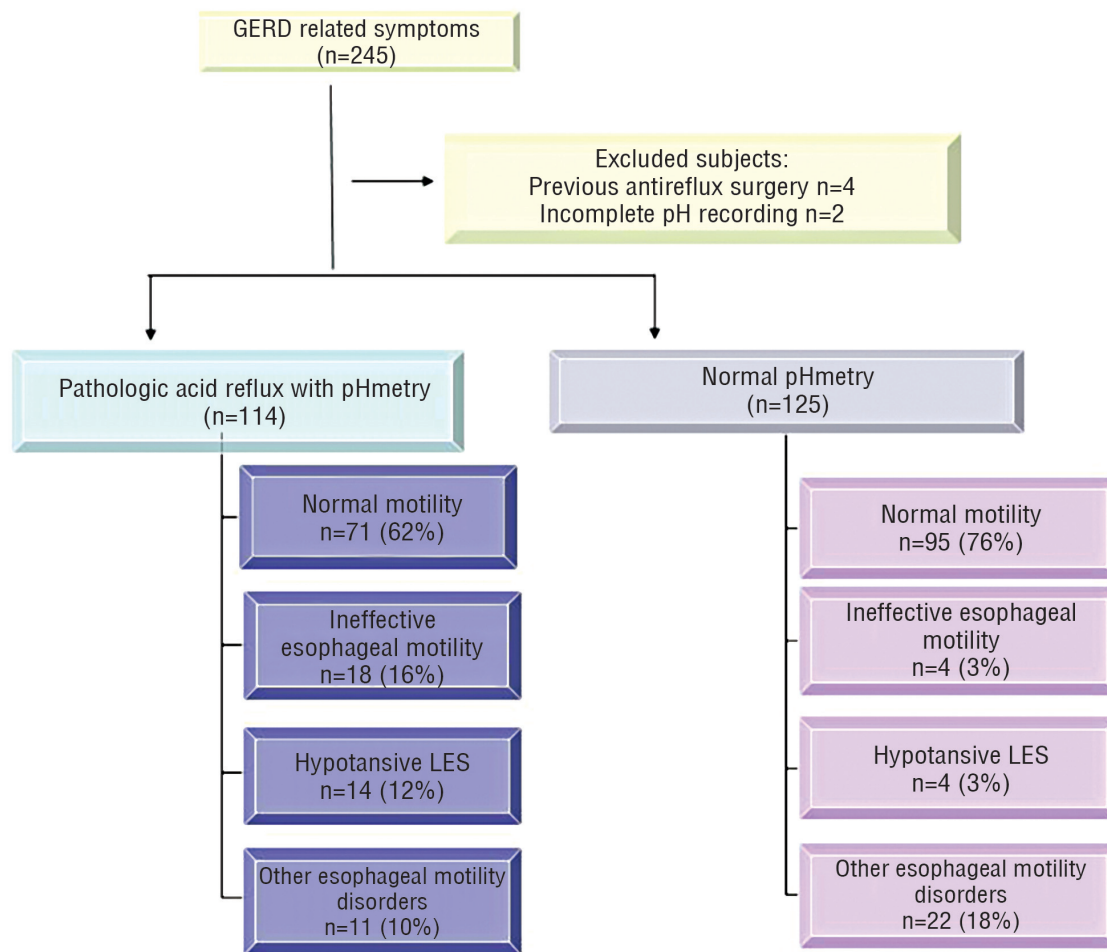


Figure 1. Enrollment and distribution of study patients according to pHmetry findings and motility abnormalities.
LES: Lower esophageal sphincter

cracker esophagus (n=13), hypertensive LES (n=6), nonspecific esophageal motility (n=1), and diffuse esophageal spasm (n=2) were also diagnosed (Figure 2).

In patients in the pathologic reflux group, BMI scores were higher than in patients with normal pH-metry (27 ± 3.5 versus 24.8 ± 3.5 ; $p < 0.05$). This difference was statistically significant (Figure 3).

Upper endoscopic evaluation was available in 80/114 in the pathologic reflux group and in 72/125 in the normal pH-metry group. Esophagitis was found in 40 (50%) and 18 (33%) pathologic and non-pathologic reflux groups, respectively. The difference was statistically significant ($p < 0.05$).

Comparison of Normal Motility and IEM Groups

Another aspect of our study was performed with comparison of normal motility patients and IEM patients.

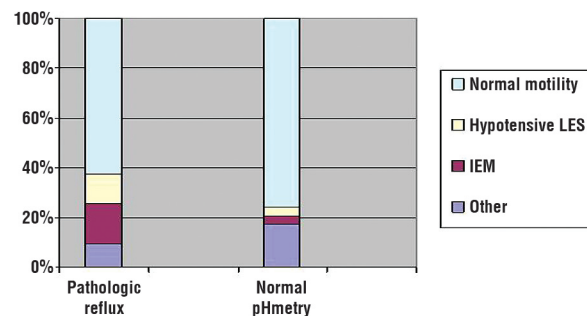


Figure 2. Manometric results of patients with pathologic and normal pH metric values. (LES: Lower esophageal sphincter. IEM: Ineffective esophageal motility.)

The entire group was reexamined according to manometric results. Of the 239 patients, 166 were found to have normal motility and 22 were found to have IEM. The IEM subjects were significantly older than the normal motility subjects (mean age:

50.6±3.0 in the IEM group and 42.6±0.9 in the normal motility group; $p<0.05$). Sex distribution did not differ between the IEM and normal motility subjects (45.5% females in the IEM group versus 51.2% females in the normal motility group; $p>0.05$).

Although BMI was higher in subjects with IEM, the difference was not significant (27.5±3.3 versus 26±3.9; $p>0.05$) (Figure 4).

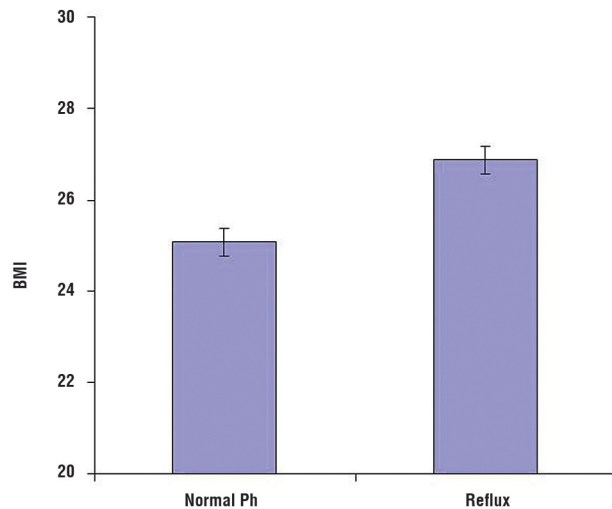


Figure 3. Comparison of BMI in functional reflux group and pathologic reflux group. Pathologic reflux patients have higher BMI than functional reflux patients ($p<0.05$). (BMI: Body mass index)

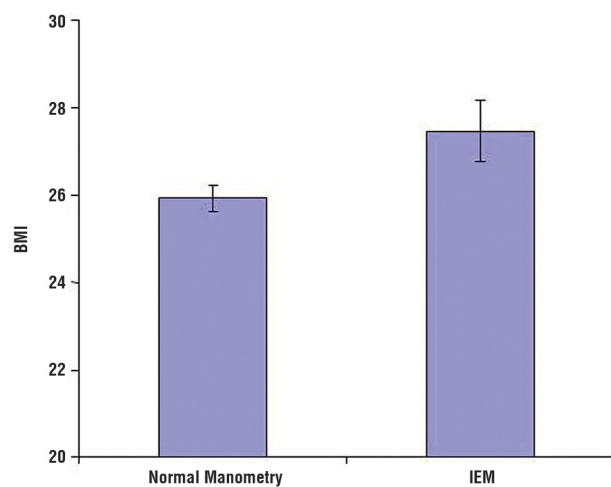


Figure 4. Comparison of BMI in normal manometry and IEM group. In IEM group BMI is higher than the normal manometry group. (BMI: Body mass index. IEM: Ineffective esophageal motility)

The LES pressure was lower in the patients with IEM than in patients with normal esophageal motility (16.2±1.4 versus 19.7±0.5; $p<0.05$) (Figure 5).

Pathologic reflux was found in 71/166 (42.8%) in the normal motility group and in 18/22 (81.8%) in the IEM group ($p<0.05$).

Patients with IEM had significantly ($p<0.05$) higher esophageal acid exposure (10.3±1.5%) compared with those without IEM (4.9±0.4%). This difference was also found significant in both supine and upright positions (Figure 6).

Although endoscopy results for the entire group were not available, erosive esophagitis was found

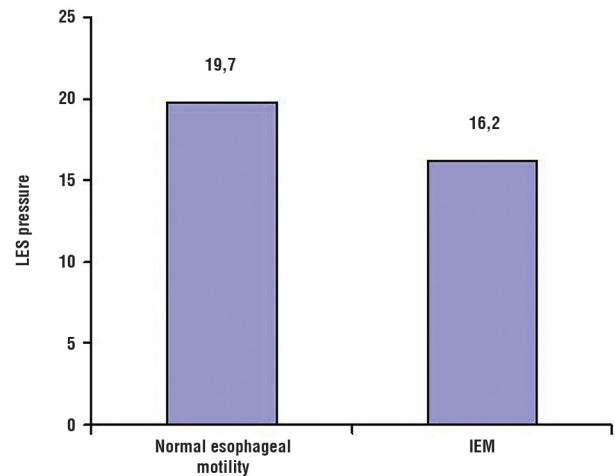


Figure 5. Comparison of LES pressure in normal esophageal motility and IEM patients. (LES: Lower esophageal sphincter. IEM: Ineffective esophageal motility)

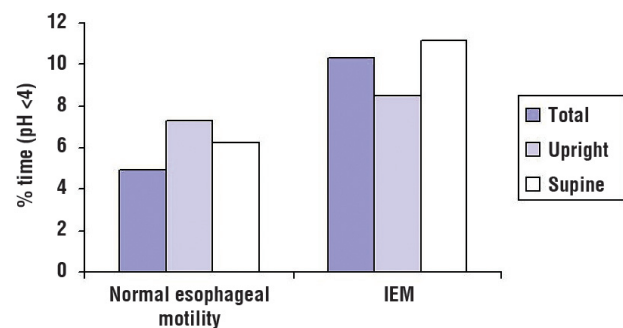


Figure 6. Relationship between esophageal acid exposure (% time esophageal pH below 4) and esophageal motility. Patients with IEM had significantly longer acid exposure during supine, upright and total periods (* $P < 0.05$ vs. no IEM). (IEM: Ineffective esophageal motility)

in 7/14 (50%) in the IEM group and in 38/104 (37%) in the normal motility group.

DISCUSSION

Ineffective esophageal motility (IEM) is frequently diagnosed in GERD patients, but whether this abnormality is secondary to acid-induced pathologic injury to the esophagus or is the reason for the GERD is still controversial (6). Our study indicated that IEM was associated with GERD, as defined by ambulatory pH monitoring. In addition, all the variables for GER were higher in the patients with IEM than those with normal esophageal motility. Patients with IEM had significantly higher esophageal acid exposure compared with those without IEM, and this difference was observed in both supine and upright positions. We also examined the association between IEM and BMI. Patients with IEM had higher BMI than those with normal motility, but the difference did not reach statistically significant levels.

An association between esophageal peristaltic dysfunction and reflux esophagitis is already known (3). The IEM term was first proposed in Leite *et al.*'s (4) article and was found more appropriate and accurate by others. Some studies confirmed an association of GERD with IEM. In one study, IEM was found to be an independent risk factor for reflux esophagitis after controlling for potential confounding factors, such as a low LES pressure, hiatus hernia, and male sex (6). In another study performed by Vinjirayer *et al.* (13), the authors do not illustrate that IEM was the major determinant of abnormal esophageal acid exposure, but they interpreted that their data did not disprove some association between GERD and IEM. Although it was not proven in all studies, in two large series of patients with confirmed GERD, mucosal injury was described to be more severe (6,14).

Another aspect of this point was investigated by Fornari *et al.* (6) and demonstrated that only severe IEM proved to be independently associated with supine prolonged clearance and increased esophageal acid exposure. Patients with GERD and mild IEM have similar esophageal clearance function and acid exposure compared with patients without IEM.

It is unclear whether IEM is a primary motor disorder or a secondary abnormality due to chronic inflammation. Experimental studies have shown

that acid-induced esophageal inflammation can lead to severe but reversible hypomotility (16,17). However, in patients with chronic erosive GERD, healing of esophagitis with medical or surgical treatment is not associated with complete recovery of the esophageal dysmotility, suggesting a secondary, irreversible motor abnormality or a primary phenomenon (17-20).

Another study, which evaluated the relationship between acid and nonacid reflux and esophageal motility, found that esophageal motility of patients with nonacid reflux was predominately normal, while IEM was frequently seen in acid reflux (21). This may enhance the interpretation of our results. Although we included patients with reflux symptoms to our study, we diagnosed 114/239 patients with acid reflux according to pH-metry analysis. We may speculate that the rest of the subjects ($n=125$) is a combined group of patients with nonacid reflux and functional heartburn. In both cases, such a conclusion can be made that IEM was more common in patients with acid reflux.

In our study, we also found hypotensive LES was the second most common esophageal motility abnormality in GERD. This finding was compatible with the other studies, one of which was performed by Rios *et al.* (22) and demonstrated that hypotensive LES with or without esophageal motor abnormalities was found in more than one-third of GERD patients. They also comment that IEM was the disorder most strongly related to reflux.

We assessed the relationship between BMI and reflux and also between BMI and IEM. We observed that patients with acid reflux defined by ambulatory pH monitoring have higher BMI than patients with normal pH-metry. Higher esophageal acid exposure and higher DeMeester scores were demonstrated in obese subjects (7,23). Recent studies on the relation between obesity and esophageal motility provide conflicting results. Kuper *et al.* (24) described lower values of LES pressure and esophageal body contraction amplitude in morbidly obese patients compared to non-obese individuals, whereas Schneider and colleagues (25) found higher contraction amplitude in obese subjects. In our study, we found that patients with IEM had higher BMI values.

Our study has a number of limitations. We included patients with persistent reflux symptoms whom referred to our clinic, and we analyzed the records retrospectively. We categorized patients

based on ambulatory pH-metry results. The ambulatory pH monitoring is not 100% accurate and it has a sensitivity of about 70%, such that some of our patients may have been misclassified (26). In a new technology, multichannel intraluminal impedance (MII) can detect the nonacid or weakly acidic reflux events, which cannot be detected by pH electrodes (27,28). Unfortunately, we could not use this state of the art technique for our study, but we included a large number of cases (239 cases), so the probability of misclassification was probably lessened.

In conclusion, we found that 38% of the acid reflux patients had abnormal esophageal motility, and the major esophageal motility abnormality was IEM. Not only did acid reflux patients have a higher incidence of IEM than the functional heartburn patients, but patients with IEM also had significantly more esophageal acid exposure in both supine and upright positions. It seems difficult to determine whether GERD is a primary factor or IEM. However, in both cases, we comment that if IEM exists, GERD is more severe and it is related to the severity of IEM.

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