Aim: To assess the correlation between esophageal dysmotility, characterized as inefficient esophageal motility (IEM), and the presence of pathological acid reflux due to a structurally defective lower esophageal sphincter (LES), hiatus hernia (HH), or esophagitis in patients with suspected gastroesophageal reflux disease (GERD). Methods: 311 patients referred for GERD diagnostic procedures in a gastroesophageal motility laboratory were included in the study. Patients underwent an interview regarding their clinical symptoms, upper endoscopy (UE), stationary esophageal manometry, and 24-h esophageal pH-metry. The following risk factors of patients in the negative pH-metry group were compared to those in the positive pH-metry group: IEM, defective LES, HH, and esophagitis. The association between IEM and positive pH-metry results was first assessed by means of univariate analysis and later determined with multivariate logistic regression analysis. Results: Out of the total of 311 studied patients, 208 met the inclusion criteria; 88 had normal and 120 had positive pH-metry results. Univariate analysis revealed that the occurrence of IEM, defective LES, and HH was significantly greater in the positive pH-metry group. Following logistic regression analysis, the occurrence of IEM remained significantly greater in the positive pH-metry group. Conclusions: IEM is associated with the presence of abnormal acid reflux, as assessed by 24-h esophageal pH-metry, regardless of the presence of defective LES, HH, or esophagitis.

Key words: gastroesophageal reflux disease, ineffective esophageal motility, esophageal manometry, 24-hour esophageal pH-metry

INTRODUCTION

Gastroesophageal reflux disease (GERD), defined as a chronic pathology resulting from the reversed flow of gastroduodenal contents into the esophagus, causes a variety of symptoms that can severely interfere with patients’ quality of life. It is a very common disease, affecting approximately 20% of the adult population in Western countries1–3.

Esophageal motility dysfunction, known as ineffective esophageal motility (IEM), occurs in 40%–60% of patients with GERD and is associated with a decrease in esophageal clearance function4,5. IEM causes a delay in acid clearance, leading to a longer contact time between the acid and the esophageal mucosa. Chronic acid reflux can also result in alterations of the esophageal muscle fibers, lower esophageal sphincter (LES), as well as the esophageal body6. IEM is a late finding of GERD, and there is evidence of amelioration of the condition following therapeutic intervention6–9. A positive correlation has also been observed between the degree of dysmotility and the severity of the esophageal lesion; i.e., the worse the motor function, the more severe the esophagitis10.

The association between hiatal hernias (HH) and reflux esophagitis is well-established. In patients with HH, there is a cranial dislocation of the distal esophageal high-pressure zone at the gastric junction, moving the LES towards the chest and causing structural changes in the LES that leads to pathological reflux. Among the most notable structural changes are decrease in the resting pressure and shortening of the LES, accompanied by the loss of its intra-abdominal component6,10–16.

There is also a correlation between HH and IEM, with a higher incidence of IEM in patients with HH. The mechanisms leading to this association have not been fully elucidated6,14,15,17,18.

Currently, little is known about the correlation between acid exposure in the distal esophagus and esophageal dysmotility, or other esophageal body motor changes in patients with GERD. Therefore, the aim of this study was to evaluate the correlation between pathological acid exposure and presence of IEM in patients with GERD.
METHODS

Patients

Between January 2005 and December 2007, we prospectively evaluated 311 patients with symptoms of GERD. These patients were referred to the digestive motility laboratories of the Instituto do Aparelho Digestivo and the Hospital de Clínicas in Porto Alegre, Brasil. Data were prospectively obtained regarding symptoms, upper endoscopy (UE), esophageal stationary manometry, and 24 h pH-metry findings.

Inclusion and Exclusion Criteria

The trial included patients with GERD symptoms who were not using antireflux medication and who agreed to a complete diagnostic evaluation. It excluded patients whose manometry results indicated esophageal motor disorders (achalasia, nutcracker esophagus, diffuse esophageal spasm, or sclerodermia) and patients who had undergone a previous surgical procedure in the esophagus, stomach, or thoraco-abdominal region. Of the 311 patients that we initially evaluated, 103 patients were excluded: 40 patients had undergone previous antireflux surgery, one had a previous thoracic-abdominal, and one had underwent bariatric procedure, 35 had not completed the proposed evaluation, and 7 were using medications to treat GERD symptoms (proton pump inhibitors or prokinetics). There were also 8 patients with achalasia, 5 with diffuse esophageal spasm, 5 with nutcracker esophagus, and one patient with systemic lupus erythematosus. Therefore, overall 208 patients were included in the trial.

Clinical Manifestations

All patients were questioned about the presence or absence of GERD-related symptoms: pyrosis, regurgitation, dysphagia, cough, asthma, dysphonia, chest pain, globus pharyngeus, and throat clearing. The presence of symptoms was regarded as positive when symptoms occurred at least weekly.

Upper Endoscopy

All of the patients included in the trial underwent a UE prior to the stationary manometry. Patients were classified according to the Los Angeles classification. The degree of esophagitis was not taken into account for statistical analysis. We also analysed the presence or absence of HH. It was considered to be present when the upper border of the rugal folds, an endoscopic marker that characterizes the esophageal-gastric junction, was =2 cm above the diaphragmatic impingement.

Esophageal Stationary Manometry

We performed stationary esophageal manometry to assess the basal pressure, thoracic and abdominal extension, and relaxation pressure of the LES. We used a Dynapack MPX 816 manometry system (Dynamed, Sao Paulo, Brazil) with an eight-channel water perfusion catheter, marked at each centimetre. After the patient had fasted for at least 6 h, the pull-through technique was applied with the patient positioned in the supine position. After the intragastric positioning of the catheter was verified, the LES was firstly observed. The LES resting pressure was assessed immediately after the pressure inversion point at the mean expiratory point. The LES was considered to be structurally defective when at least one of the following findings was present: <6 mmHg of the resting pressure, cm of the total length of LES, <2 cm of abdominal length. The esophageal body was assessed with pressure sensors positioned at 3, 8, and 13 cm above the proximal edge of the LES, while the patient swallowed water ten times (5 ml each time) at 30 s intervals. Pressure curves were recorded and measured by the Gastromaster program (Dynamed, Sao Paulo, Brazil). An IEM diagnosis was made when there were ≥30% nonperistaltic waves, or when the mean amplitude in the distal esophagus was <30 mmHg.

24-hour Esophageal pH-metry

We performed the pH-metry tests with a portable pH-recording device (Sigma Instruments, Belo Horizonte, Brazil), which was connected to a catheter with an antimony electrode. Another external reference sensor was connected to the patient’s chest. After calibration in pH 4 and 7 solutions, the catheter was introduced through one nostril until it was 5 cm above the proximal edge of the LES (identified on manometry). Patients were instructed to pursue their normal activities and to keep diaries describing when their meals began and ended, as well as their postural changes (supine or orthostatic) and the occurrence of symptoms throughout the 24h period. On the following day, the device was removed and the data were transferred to a computer program for interpretation (Esograph 4.0; Sigma Instruments, Belo Horizonte, Brazil). Pathological acid reflux was considered to be present when the DeMeester score was higher than 14.7.

Statistical Analysis

We analyzed the following variables: age, gender, clinical manifestations (pyrosis, regurgitation, dysphagia, chronic cough, asthma, dysphonia, chest pain, globus pharyngeus, and throat clearing), presence of HH, esophagitis, IEM, and defective LES. In addition, during the 24 h esophageal pH-metry, we measured the presence of pathological acid reflux.

We used the Student’s t-test to compare the noncategorical mean variables. For the categorical variables, we used the chi-square test. The effects of the IEM, defective LES, HH, and esophagitis on the 24 h esophageal pH-metry results were primarily calculated using univariate logistic regression analysis, and were expressed as odds ratio (OR) with a 95% confidence interval (CI). Subsequent multivariate logistic regression analyses were carried out to assess the association between the pH-metry results and IEM while controlling for defective LES, HH, and esophagitis. These data were expressed as adjusted odds ratio (ORa) with a 95% CI. The OR was considered...
to be statistically significant when the 95% CI value was above 1. A result was considered to be statistically significant if $p < 0.05$. The analyses were made using the SPSS statistical program version 15.

**RESULTS**

The mean age of the 208 patients included in the trial was 47 years (range 17–82 years). There was no significant difference between the mean age distributions among the pH-metry negative (mean age 46.5 years) and the pH-metry positive groups (mean age 47.5 years) ($p=0.619$). There were 131 female (63%) and 77 male (37%) patients (Table 1). There was no statistically significant difference in the gender distribution in the positive and the negative pH-metry groups ($p=0.112$). Regarding clinical manifestations, there was also no statistically significant difference in the distribution of symptoms in the negative and positive pH-metry groups. The distribution of the individuals in both pH-metry groups, is shown in Table 2, taking the factors under study into the account.

Manometric evaluation revealed that 16 (7.7%) out of 208 patients presented with IEM; a significantly higher number of patients with IEM were in the positive pH-metry group (15 patients; 93.8%). There was also a significant difference in the distribution of patients with a defective LES; out of 52 patients (25%) with a defective LES, 39 (75%) were in the positive pH-metry group. Endoscopy revealed that HH was present in 98 patients (47.1%); 64 (65.3%) of these patients were in the positive pH-metry group, while 34 (34.7%) were in the negative pH-metry group, indicating a statistically significant difference ($p = 0.049$). Esophagitis was present in 68 (32.7%) patients; 46 (65.3%) were in the positive pH-metry group and 22 (32.4%) were in the comparison group. However, this was not a statistically significant difference ($p = 0.052$).

Using logistic regression analysis (Table 3), we assessed the association of GERD with the following risk factors: IEM, defective LES, HH, and esophagitis. When assessed in a univariate manner, i.e., disregarding the influence of other risk factors in the result, patients with IEM were more likely to have a positive 24 h pH-metry result compared to patients without IEM (OR=12.13, $p < 0.05$). When multivariate analysis was applied; i.e., when IEM was assessed while controlling for the presence of defective LES, HH, and esophagitis, the ORa for a positive pH-metry result was 8.89, a statistically significant difference ($p<0.05$). When the LES was defective, the OR decreased from 2.78 in the univariate analysis ($p <0.05$) to ORa 2.23 after logistic regression; statistical significance was maintained ($p<0.05$). With HH as the risk factor, the OR decreased from 1.82 ($p<0.05$) in the univariate analysis to ORa 1.43 ($p>0.05$) after the multivariate analysis; statistical significance was lost.

Esophagitis, as the risk factor had a univariate analysis OR of 1.86 and a multivariate analysis ORa of 1.6 after the multivariate analysis; neither were statistically significant ($p>0.05$).

**TABLE 1**

<table>
<thead>
<tr>
<th>SAMPLE CHARACTERISTICS</th>
<th>pH metry (-)</th>
<th>pH metry (+)</th>
<th>Total patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>46.5</td>
<td>47.5</td>
<td>47</td>
<td>0.619</td>
</tr>
<tr>
<td>Female</td>
<td>n=88 (42.3%)</td>
<td>n=120 (57.7%)</td>
<td>n=208 (100%)</td>
<td>0.112</td>
</tr>
<tr>
<td>Male</td>
<td>27 (30.7%)</td>
<td>50 (41.7%)</td>
<td>77 (37%)</td>
<td></td>
</tr>
<tr>
<td>Symptoms (n,% )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrosis</td>
<td>58 (65.9%)</td>
<td>85 (70.8%)</td>
<td>143 (68.8%)</td>
<td>0.454</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>38 (43.2%)</td>
<td>61 (50.8%)</td>
<td>99 (47.6%)</td>
<td>0.326</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>14 (15.9%)</td>
<td>28 (23.3%)</td>
<td>42 (20.2%)</td>
<td>0.223</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (23.9%)</td>
<td>36 (30%)</td>
<td>57 (27.4%)</td>
<td>0.349</td>
</tr>
<tr>
<td>Asthma</td>
<td>8 (9%)</td>
<td>8 (6.7%)</td>
<td>16 (7.7%)</td>
<td>0.602</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>12 (13.6%)</td>
<td>24 (20%)</td>
<td>36 (17.3%)</td>
<td>0.268</td>
</tr>
<tr>
<td>Chest pain</td>
<td>12 (13.6%)</td>
<td>17 (14.2%)</td>
<td>29 (13.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Globus pharyngeus</td>
<td>12 (13.6%)</td>
<td>22 (18.3%)</td>
<td>34 (16.3%)</td>
<td>0.489</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>41 (46.6%)</td>
<td>53 (44.2%)</td>
<td>94 (45.2%)</td>
<td>0.779</td>
</tr>
</tbody>
</table>
The presence of symptoms suggesting reflux, both typical and atypical, usually leads to a diagnostic investigation of GERD. However, the presence of these symptoms is not sufficient to establish GERD, because they are common to a wide array of diseases. Thus, additional tests are needed when GERD is suspected. In our study, analysis of GERD symptoms confirmed that there was not a statistically significant difference in their distribution between positive and negative pH-metry groups.

The association of IEM and esophagitis has been recognized for more than twenty years, and has been systematically confirmed by several trials. Recently, Fornari et al. conducted a multivariate regression analysis in 387 patients with GERD and concluded that patients with esophagitis are 1.7 times more likely to present with IEM than patients without esophagitis. Diener et al., in an analysis of 1,006 patients with GERD, reported that the group with IEM included individuals with more severe endoscopic lesions. In 2003, Chrysos et al. observed that in 147 GERD patients, the more-severe the esophageal lesions was detected by endoscopy, the greater was the decrease in esophageal motor function. The presence of pathological acid reflux, as well as greater difficulty eliminating refluxate into the gastric lumen (worse clearance capacity), indicates that IEM is associated with HH; cranial dislocation of the LES that interferes with contraction amplitude of the distal esophagus (worse clearance capacity).

The association between HH and IEM has also been studied by several authors. Xenos et al. evaluated HH in 51 patients with symptoms suggestive of GERD and concluded that the HH was associated with the presence of pathological acid reflux. DeMeester et al., evaluating 102 patients with GERD using manometry and 24h pH-metry, concluded that patients with HH have a greater incidence of exposure to pathological acid reflux, as well as greater difficulty eliminating refluxate into the gastric lumen (worse clearance capacity).

The association between HH and GERD has been studied extensively. In early GERD trials, the association between HH and GERD was so strong that they were thought to be the same entity. In the present trial, after univariate analysis there was a statistically significant difference with regard to the presence of HH in the positive and negative pH-metry groups; the positive pH-metry group included most individuals with HH. However, when we conducted multivariate regression analysis controlling for the presence of HH due to other risk factors, this difference was not replicated. There is a widely held belief that HH is an important risk factor in the pathogenesis of GERD, leading to a decline in distal esophageal motor function, a decrease in clearance capacity, and structural changes to the LES that interfere with its function. However, the results of our trial did not demonstrate an exclusive association between the presence of HH and greater acid exposure, as measured by pH-metry.

The presence of a structurally defective LES is generally associated with HH; cranial dislocation of the LES due to HH can lead to structural changes in the LES. A defective LES predisposes to pathological acid reflux of gastric contents into the lumen of the distal esophagus; as has been clearly demonstrated in the literature.
structural changes are present in the LES, GERD is more advanced, whereas the early mechanisms associated with the genesis of reflux are the transient relaxations of the LES15,17,27,28. We verified the positive association between defective LES and positive pH-metry in our trial, confirming several previous reports stating that a defective LES is associated with pathological acid reflux14,17,18.

Although GERD generates a large number of trials in the field of gastroenterology, during an extensive review of the GERD literature, we found only one reference regarding the association between esophageal dysmotility and pH-metry. In a logistic regression analysis to study the factors involved in the genesis of reflux esophagitis, Cadiot et al.20 concluded that the number of refluxes with a duration greater than 5 min (which characterizes difficulty in esophageal clearance), as determined by 24 h pH-metry, is the main risk factor for the occurrence of reflux esophagitis. In the present trial, we observed a clear association between IEM and positive pH-metry; of all the patients who presented with IEM, 93% were in the positive pH-metry group in the univariate analysis (OR = 12.43). Most importantly, following multivariate analysis, this association continued to be strong (ORa = 8.89). This association reinforces the need for a complete evaluation of this patients subgroup, extending beyond a simple clinical and endoscopic evaluation.

A number of recent publications reporting the results of surgical treatment for GERD have provided evidence for improved motor function of the esophageal body once it is no longer being regularly exposed to refluxed gastric contents29-32. This indicates that motor dysfunction is likely a result of lesions on the esophageal wall caused by refluxate, rather than a primary cause of GERD that facilitates the occurrence of reflux. Therefore, IEM can be defined as a late-stage complication of GERD.

In conclusion, the presence of gastric acid in the esophageal lumen, as determined by 24-hour pH-metry, was associated with a 9-fold greater likelihood of esophageal dysmotility, most of which was of the IEM type.

### Table 3

**Multivariate Logistic Regression Analysis of 24h Esophageal pH Metry in Patients with IEM, Defective LES, HH, and Esophagitis**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR (95% CI)</th>
<th>ORa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEM</td>
<td>12.43 (1.72-90.05)*</td>
<td>8.89 (1.13-70.15)*</td>
</tr>
<tr>
<td>Defective LES</td>
<td>2.78 (1.38-5.57)*</td>
<td>2.23 (1.07-4.64)*</td>
</tr>
<tr>
<td>HH</td>
<td>1.82 (1.04-3.17)*</td>
<td>1.43 (0.79-2.6)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>1.86 (0.98-3.61)</td>
<td>1.6 (0.84-3.04)</td>
</tr>
</tbody>
</table>

*p<0.05

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**SUMMARY**

**KORELACIJA IZMEĐU PATOLOGIJSKOG GASTROEZOFAGEALNOG REFLUKSA I NEEFFEKTIVNOG MOTILITETA JEDNJAKA**

Cilj: Procena korelacije izmedju poremećaja motiliteta jednjaka, okarakterisanog kao neefektivan motilitet jednjaka (NMJ) i prisustva patološkog gastroezofagealnog reflikusa uzrokovanih tromočlano izloženim nihovednim faktorom (DES), hernijom hijatusa jednjaka ili ezofagitisu, kod bolesnika sa suspektnom gastroezofagealnom reflikslom bolesću (GERB).


Rezultati: Od ukupno 311 ispitivanih bolesnika, 208 je uključeno u studiju, od kojih je 88 imalo normalne a 120 patološke vrednosti na ezofagealnom pH metriju. Univerzalna analiza je ukazala da je učestalost NMJ, nefunkcionalnog DES-a, kao i prisustvo hernije hijatusa jednjaka značajno veća kod bolesnika sa pozitivnim vredностima na 24-časovnom pH metriju. Proračun logističke regresione analize, prisustvo NMJ je ostalo značajno češće u grupi bolesnika sa pozitivnom ezofagealnom pH metrijom.

Zaključak: NMJ je direktno povezana sa prisustvom patološkog kiselinskog reflikusa u jednjaka, dokazanog 24-časovnom pH metrijom, bez obzira na prisustvo nefunkcionalnog DES-a, hernije hijatusa jednjaka ili endoskopski vidljivog ezofagitisu.

Ključne reči: gastroezofagealna reflikslna bolest, neefektivan motilitet jednjaka, manometrija jednjaka, 24-časovna pH metrija jednjaka
REFERENCES


