24-Hour Ambulatory pH-Metry in Patients with Refractory Heartburn: A Prospective Study

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a chronic condition that affects a large proportion of population. The aim of our study was to determine what percentages of patients with persistent heartburn on acid suppressive therapy have evidence of reflux disease while off acid suppressive therapy. Methods: In a prospective study 48 patients with refractory heartburn from Taleghani Hospital were enrolled who had been on a double dose of proton pump inhibitor (PPI) for 8 weeks without improvement. Because of low index of suspicion for GERD as an etiology, all the patients underwent 24h pH-metry while off PPI. The variables of pH-metry such as the fraction time of pH <4 were evaluated by comparing to normal volunteers. Results: The mean “number of acid refluxes” was 49.98 in upright position and 6.29 in supine position. The mean “longest acid reflux” duration was 2.98 minutes in upright and 3.13 minutes in supine position. The total time fraction of pH <4 was 2.97% in upright position, 1.2 % in supine position and 2.74% in postprandial state. The mean DeMeester score was 10.06 (SD=10.48). However, the difference in the total fraction of time with pH <4 was not significant. Conclusion: Our study showed that most of the patients with refractory heartburn did not have acid reflux. Patients with refractory heartburn often do not have evidence of reflux disease on pH monitoring, thus evaluating these patients should be performed while on acid suppressive therapy (using impedance-pH monitoring) in order to clarify the relationship between symptoms and acid and non-acid reflux.

Keywords

of most clinical trials [5]. Limited prospective studies have demonstrated normalization of esophageal pH with q.i.d. PPI therapy in over 90% of patients with typical reflux symptoms [6].

The previous consensus was to consider the percentage time with the intraesophageal pH below 4 as the most useful outcome measure in discriminating between physiological and pathological esophageal reflux [7]. Distal esophageal acid exposure can be quantified using the DeMeester score (DS) or percentage time pH=4. The original scoring system devised by Johnson and DeMeester [8] examined six variables (percent total time pH was <4, percent upright time pH was <4, percent recumbent time pH was <4, number of reflux episodes, number of reflux episodes with pH <4 for five minutes, and the period of the longest single acid exposure episode) and calculated a composite score according to a formula dependent on the deviation of each of these variables from normal values. With the exception of the overall number of reflux episodes which proves to be poorly reproducible, each of these derived values has merit, at least in some circumstances. However, there is now a consensus that the percent time with pH <4 (esophageal acid exposure time) is the most useful discriminator between physiological and pathological reflux. Other variables which vary with the esophageal acid exposure time, are less reproducible, and have less discriminatory power. Nonetheless, most commercially available software packages analyze pH data for all of the six scoring variables identified by Johnson and DeMeester [8]. In addition to these parameters, the symptom index (SI) is used to evaluate the association of symptoms and acid reflux. The SI is defined as the number of reflux – related symptom episodes divided by the total number of reflux episodes, expressed as a percentage. However, the SI is not validated against an independent criterion of diagnostic accuracy such as symptomatic response to antireflux therapy.

The main goal of the present study was to determine what percentages of patients with persistent heartburn on acid suppressive therapy have evidence of reflux disease while off acid suppressive therapy.

**Material and Methods**

We conducted the study on 48 patients complaining of heartburn referred to the Research Center of Gastrointestinal and Liver Disease, Department of Esophageal pH-metry and Manometry, Taleghani Hospital, Tehran, Iran, while off therapy (off PPI) for one week. The patients with a history of persistent heartburn despite the use of 40 mg per day omeprazole for at least 8 weeks and with no response to treatment were included in the study as the group of “low index of suspicion for GERD”. The patients with heartburn which had improved only partially with doubling the dose of PPI were considered as “a high index of suspicion for GERD” and were excluded from the study. Since the majority of our patients had not undergone endoscopy, endoscopic data were not included among the variables. The data were gathered during two years in a Taleghani hospital. According to literature, they were told that they had refractory GERD. The patients underwent ambulatory pH monitoring for 24 hours.

Ambulatory pH monitoring was performed with a transnasally placed catheter to the distal esophageal mucosa. In this study pH-metry was done with a Metronic, Polygram (version 2.05) and by a gastrointestinal (GI) specialist with special interest and experience in esophageal reflux and motility diseases. The pH of buffering solutions was used to calibrate the pH sensors at the beginning of the esophageal acid monitoring. The device has two sensors; the pH sensors are coupled with compact, portable data loggers, and computerized data analysis. The catheter type pH electrode was positioned 5 cm above the manometrically defined upper limit of the lower esophageal sphincter. Esophageal pH was recorded in supine, postprandial positions. The variables that were important for the study were: number of acid reflexes, longest acid reflux, the fraction of time pH below 4 (%) and each of these variables related to upright, supine, during meal or postprandial were recorded. We used the DeMeester score for evaluation of acid reflux. A score more than 14.7 was considered abnormal acid reflux. A 24-hour esophageal pH study that samples intraesophageal pH every six seconds results in the generation of 14,400 data points in addition to the event marker data. We compared the results of the pH-metry of our patients with the esophageal acid exposure in 50 healthy volunteers in the DeMeester study [9].

The Ethical Committee of the Shahid Beheshti University of Medical Sciences approved the study protocol. A consent form was completed by each patient before any procedure.

**Statistical Analysis**

The Student’s t-test was used to compare means of continuous variables. Comparisons of the distribution of categorical variables between two study groups were performed using the Chi-squared test. Continuous variables are presented as mean ± standard deviation, and other parameters as frequency and percentage. Because of the number of patients in similar studies as well as the few cases found to have the inclusion criteria of our study, the sample size in our study was calculated as 50 patients. The statistical package SPSS 15.0 was used for data analysis. A P-value of 0.05 or less was considered statistically significant and all reported P values were two sided.

**Results**

The study comprised 48 patients (33% F, 67% M) who fulfilled the inclusion criteria and all of them had 24-hour esophageal pH monitoring. The mean age of the patients was 37 ± 11 years (range 17-64).

The mean number of acid reflexes was 51.7% in upright position, 9.5% in supine position, 13.9% during meal and 33.4% in postprandial state.

The mean duration of the longest acid reflux was 3 min in upright and 4.8 min in supine position, 1.1 min during
The fraction of time (%) during 24 hour pH metry pH <4 was 3.1% in upright position, 2.2% in supine, 5.2% related to meal time and 2.8% in postprandial state.

The mean of the DeMeester score was 12.3 ± 18.8. The max and min of the DeMeester score were 51% and 5%, respectively. A DeMeester score more than 14.7 that represents abnormal acid reflux, was observed in 22.8% of patients. A SI more than 50% was considered positive. Positive SI as well as a DeMeester score more than 14.7 was seen in14.5% of patients. A negative SI and DeMeester score less than 14.7 was detected in 66.7% of patients.

We compared the results of the pH-metry of our patients with findings from the pH-metry of 50 normal healthy volunteers performed by DeMeester [9]. The result of postprandial pH was also compared with another pH recording of normal volunteers. Statistical analysis, comparing pH-metry variables between our patients and healthy volunteers are shown in Tables I and II.

The test showed statistically significant differences for the DeMeester score. Symptom-reflux correlation in our patients is evidenced in Table III.

### Discussion

In this study, according to the low probability of acid reflux in patients with refractory heartburn while using PPIs, we performed pH-metry in off PPI (for at least one week). The results showed that refractory heartburn in the majority of cases is not due to acid reflux.

Confirmed the low index of suspicion for patients with refractory heartburn with double dose PPI, Charbel et al [10] reported that 30% of patients with either typical or extraesophageal symptoms had abnormal pH monitoring on q.i.d. PPI therapy. These proportions fell to 7% for the typical and 1% for the extraesophageal patients taking b.i.d. PPI and concluded that the likelihood of an abnormal esophageal pH for symptomatic GERD patients on b.i.d. PPI is very small [10]. In this group of patients failing b.i.d. PPIs, causes other than GERD should be sought.

Response to PPIs does not confidently establish the diagnosis of GERD when GERD has been defined using currently accepted reference standards. This raises the possibility that many patients who respond to a PPI (and are therefore frequently maintained on a PPI) are in fact receiving the equivalent of expensive long-term placebo treatment, or have an acid-responsive disorder other than GERD. On the other hand, the observation that 40 to 90 percent of patients with symptoms suggestive of GERD have a symptomatic response to PPIs raises the question as to what the optimal gold standard should be for defining GERD [11].

An empirical trial of therapy with full- or double-dose PPI has been suggested as a “test” for GERD. Relief of symptoms within one week of omeprazole 20 mg twice daily had a sensitivity of 75% and a specificity of 55% when compared...
with endoscopy and ambulatory pH testing [12].

In another study, using pH as the gold-standard, an omeprazole trial had a positive and negative predictive value of 68% and 63%, respectively, and when the omeprazole trial was considered the standard, the pH test had identical positive and negative predictive values. Katzka et al reported abnormal esophageal pH studies in 56% of patients with refractory heartburn and 28% of patients with atypical reflux symptoms while taking omeprazole 20 mg b.i.d. and using the stricter definition of normal as esophageal pH <4 of 1.6%

<table>
<thead>
<tr>
<th>Patients Mean (±SD)</th>
<th>Healthy volunteer Mean (±SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time at pH less than 4 (%)</td>
<td>2.210 (2.83)</td>
<td>1.5 (1.4)</td>
</tr>
<tr>
<td>Upright time at pH less than 4 (%)</td>
<td>2.97 (4.19)</td>
<td>2.2 (2.3)</td>
</tr>
<tr>
<td>Supine time pH less than 4</td>
<td>1.206 (2.63)</td>
<td>0.6 (1.0)</td>
</tr>
<tr>
<td>Number of reflux episodes</td>
<td>56.04 (45.82)</td>
<td>19.0 (12.8)</td>
</tr>
<tr>
<td>Number of reflux episodes &gt;5 min</td>
<td>0.75 (1.80)</td>
<td>0.8 (1.2)</td>
</tr>
<tr>
<td>Duration of the longest episode of reflux</td>
<td>4.81 (6.49)</td>
<td>6.7 (7.9)</td>
</tr>
<tr>
<td>DeMeester score</td>
<td>10.062 (10.48)</td>
<td>6.0 (4.4)</td>
</tr>
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</table>

Our study showed that the majority of patients with refractory heartburn did not have acid reflux as documented by the DeMeester score and fraction time pH below 4 and also had negative symptom index.

In patients with a low likelihood of GERD with no response to double dose PPI, a negative pH-metry finding while off PPI is sufficient to rule out acid reflux. We recommend esophageal impedance pH-metry to determine if there is non-acid reflux (gas or bile) to cause patients symptoms like heartburn. But in the minority of patients with a high index of suspicion for GERD and refractory symptoms and a positive DeMeester score, there is a small possibility of acid reflux, and pH-metry while on PPI would be the next step.

Because patients with refractory heartburn often do not have evidence of reflux disease on pH monitoring, evaluating these patients should be performed while on acid suppressive therapy (using impedance-pH monitoring) in order to clarify the relationship between symptoms and acid and non-acid reflux.

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Conflicts of interest

None to declare.

References


