Tailored therapy for the refractory GERD patients by combined multichannel intraluminal impedance–pH monitoring

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Abstract

Background and Aims: About 30% of patients with gastroesophageal reflux disease (GERD) are refractory to proton pump inhibitor (PPI). The reason for the PPI failure in Asian GERD patients has rarely been studied, and the therapy remained unclear. The aims were to explore the possible reasons for PPI failure and to treat these patients with the guidance of 24-h multichannel intraluminal impedance-pH (MII-pH) monitoring.

Methods: Thirty-nine consecutive patients with refractory GERD were enrolled; 24-h MII-pH monitoring was performed on PPI. The refractory GERD patients were grouped into acid overexposure, non-acid reflux, and functional heartburn after the MII-pH monitoring. Double dose of either PPI or paroxetine was administered to refractory GERD patients within different groups.

Results: The number of patients in groups of acid overexposure, non-acid reflux, and functional heartburn was 6, 12, and 21, respectively. The acid overexposure group had the most acid reflux events. Among the acid overexposure group, five (5/6) patients accomplish symptom relief with double dose of esomeprazole. For the patients in non-acid reflux group, double dose of esomeprazole made half (6/12) of the patients obtain symptom relief. For the patients in functional heartburn group, the paroxetine had relieved the symptoms in 14 patients among all the 21 patients. In total, with the guidance of MII-pH monitoring, 64.1% (25/39) of refractory GERD patients accomplished symptom relief.

Conclusions: Acid overexposure, non-acid reflux, and functional heartburn were the common reasons for persistent reflux symptoms despite PPI. With the guidance of MII-pH, a tailored therapy could resolve the persistent reflux symptoms among two-third of patients.

INTRODUCTION

Refractory gastroesophageal reflux disease (GERD), which has been defined as the lack of response to double dose proton pump inhibitor (PPI) therapy, is now a topic drew with much clinical attention.1 Although effective, the PPI has been shown to fail to control the typical reflux symptoms in about 30% of GERD patients.2 The possible factors related to the PPI failure included patients’ compliance, timing and dosing of PPI, and inadequate control of esophageal acid.2,3 Nevertheless, the most popular factor contributing to the PPI failure goes to the non-acid reflux.4–6 Non-acid reflux, contrary to acid reflux, refers to a reflux during which the esophageal pH does not drop lower than 4.7 Although rare, the non-acid reflux attributes to about 10–20% persistent symptoms in GERD patients according the recent studies, which tried to find out the reasons of PPI failure in GERD.4–6 The management of non-acid reflux is controversial. The current options include the increase of PPI dosage and the inhibition of transient lower esophageal sphincter (LES) relaxation and endoscopic and laparoscopic fundoplication. However, all the previous therapies have not been well evaluated in clinical studies. And there is individual variation concerning the choice of therapy option.

So far, the reason for the PPI failure in Asian GERD patients has rarely been studied. The therapy of refractory GERD remained unclear. Tailored therapy indicated the management of refractory GERD according to the reasons of symptom persistence with the guidance of multichannel intraluminal impedance-pH (MII-pH) monitoring. The aims of our study were to explore the possible...
reasons for PPI failure and to treat these patients with the guidance of 24-h MII-pH monitoring.

Methods

Subjects. Consecutive patients presented to the Gastroenterology Clinic, Department of Medicine, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, with ages between 18 and 70 years, who had heartburn as their predominant symptom for more than 3 months, were included. Patients must have at least three episodes of heartburn per week for the previous 2 weeks before enrollment. Both upper endoscopy and 24-h combined MII-pH monitoring were performed. Patients who had erosive esophagitis, Barrett’s esophagus, gastric or duodenal ulcer, cancer in upper gastrointestinal tract, history of operation of upper gastrointestinal tract, irritable bowel syndrome, severe cardiac or pulmonary diseases, diabetes, and rheumatic diseases were excluded. Patients were excluded if they were on nonsteroidal anti-inflammatory drugs or were unable to complete 24-h combined MII-pH monitoring. Signed informed consent was obtained from all patients. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University.

Study protocol. Esomeprazole was given to all the included patients with a dosage of 20 mg b.i.d. for 4 weeks. The therapy was defined as successful if the patient had heartburn relieved or had less than one episode of mild heartburn in the final week of therapy, otherwise defined as refractory GERD patients. Twenty-four-hour MII-pH monitoring was performed among all the refractory GERD patients in the final day of therapy. The refractory GERD patients were grouped into acid overexposure, non-acid reflux, and functional heartburn after the 24-h MII-pH monitoring. Signed informed consent was obtained from all patients. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University.

Combined multichannel intraluminal impedance-pH monitoring. Twenty-four-hour combined MII-pH monitoring was performed using a sleuth system—Multichannel Intraluminal Impedance Ambulatory System (Sandhill Scientific, CO, USA)—which includes a portable data logger with impedance-pH amplifiers and a catheter containing one pH channel and six impedance channels.

Patients were fasted for at least 8 h before recording. The recorder was calibrated using pH 4.0 and 7.0 buffer solutions. LES was located by esophageal manometry. The impedance-pH catheter was then inserted through the nostril and positioned in the esophageal body to record pH at 5 cm and impedance at 3, 5, 7, 9, 15, and 17 cm above the LES. Subjects were encouraged to maintain their normal activities and have their usual meals at normal time. But chewing gum and snacks between meals were prohibited. They were asked to remain upright during daytime and lie down only during their usual bedtime. Event markers on the data logger recorded symptoms, meal times, and postural changes.

Reflex episodes were characterized by the composition of refluxate as liquid, gas, and mixed reflux, as defined in the study of Vela M et al.8 Liquid reflux was defined as a retrograde 50% drop in impedance starting distally (at the level of the LES) and propagating to at least the next two more proximal impedance measuring segments. Gas reflux was defined as a simultaneous increase in impedance >3000 Ω in any two consecutive impedance sites with one site having an absolute value >7000 Ω in the absence of swallowing. Mixed reflux was defined as gas reflux occurring immediately before or during a liquid reflux. Reflux episodes were characterized by pH metry as acid, weakly acidic, or weakly alkaline according to a consensus report on detection and definition of gastroesophageal reflux.2 Acid reflux episodes that result in an esophageal pH drop between 4 and 7; and (3) weakly alkaline reflux: reflux episodes during which esophageal pH does not drop below 7.

Definition of group. Patients were grouped into the following: acid overexposure, non-acid, and functional heartburn, after 24-h MII-pH monitoring. The normal range for the 24-h MII-pH monitoring on esomeprazole was adopted from the study of Zerbib et al.9 Acid overexposure group was defined as either the percentage of esophageal pH less than 4 and more than 0.4% during 24-h duration on esomeprazole or the positive symptom association probability to acid reflux (>95%). Non-acid group was defined as the positive symptom association probability to weakly acid reflux or weakly alkaline reflux (>95%), or the overall reflux events were more than 57 episodes per 24 h. Functional heartburn group was defined as no pathologic reflux during 24-h MII-pH monitoring on esomeprazole.

Statistical analysis. Parametric data were expressed as mean ± standard error of means and non-parametric data as median (inter-quartile range). Comparisons among groups were performed using one-way ANOVA, non-parametric test, or Chi-square test according to different data. All P values were two-tailed with the level of significance defined at 0.05. Data analysis was performed using a standard software package (SPSS version 16.0; IBM, Armonk, NY, USA).
Result

Demographic characteristics of the refractory gastroesophageal reflux disease patients. There were 96 patients with heartburn who met the inclusion criteria. Among them, 39 patients were defined as refractory GERD patients due to persistent reflux symptom after esomeprazole therapy. Six patients were grouped into acid overexposure because of unsatisfactory control of esophageal acid reflux. Twelve patients were grouped into non-acid reflux because of the positive symptom association probability to weakly acidic reflux in nine patients and abnormal reflux events in three patients. The rest of the 21 patients were grouped into functional heartburn because there is no pathologic reflux during 24-h MII-pH monitoring on esomeprazole. The demographic characteristic of all the refractory patients was listed in Table 1.

Table 1  Demographic characteristic of refractory gastroesophageal reflux disease patients in different groups

<table>
<thead>
<tr>
<th>Gender (male : female)</th>
<th>Acid overexposure (n = 6)</th>
<th>Non-acid reflux (n = 12)</th>
<th>Functional heartburn (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.4 ± 5.7</td>
<td>43.6 ± 8.1</td>
<td>50.9 ± 7.6</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>21.6 ± 1.5</td>
<td>23.4 ± 2.1</td>
<td>23.3 ± 2.2</td>
<td>0.204</td>
</tr>
</tbody>
</table>

BMI, body mass index.

Table 2  The reflux parameters in all patients with persistent reflux symptoms

<table>
<thead>
<tr>
<th>Reflux</th>
<th>Acid overexposure (n = 6)</th>
<th>Non-acid reflux (n = 12)</th>
<th>Functional heartburn (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Median (25th, 75th) percentile</td>
<td>180 (9, 586)</td>
<td>100 (6, 1)</td>
<td>110 (3, 18)</td>
<td>0.010</td>
</tr>
<tr>
<td>Weak acid Median (25th, 75th) percentile</td>
<td>31 (5, 59)</td>
<td>45 (36, 70)</td>
<td>27 (20, 31)</td>
<td>0.064</td>
</tr>
<tr>
<td>Weakly alkaline Median (25th, 75th) percentile</td>
<td>0 (0, 21)</td>
<td>0 (0, 7)</td>
<td>0 (0, 6)</td>
<td>0.651</td>
</tr>
</tbody>
</table>

Combined multichannel intraluminal impedance-pH monitoring data in refractory gastroesophageal reflux disease patients. The MII-pH monitoring parameters were compared among the three groups (Table 2). The only difference of the parameter among the three groups lied in the acid reflux events; the acid overexposure group had the most acid reflux events. All the patients had similar weakly acidic and alkaline reflux events.

The outcome of the management of refractory gastroesophageal reflux disease. The outcome of the management of the included refractory GERD patients was listed in Figure 2. According to the planned algorithm, six patients within the acid overexposure group were administered esomeprazole in double dose (40 mg b.i.d.) for another 4 weeks. Among them, five patients accomplish symptom relief and only 1 patient still suffered from the persistent reflux symptom.

For the patients in non-acid reflux group, double dose of esomeprazole made half (6/12) of the patients obtain symptom relief, while there were six patients who need neuromodulators.

For the patients in functional heartburn group, the paroxetine had relieved the symptoms in 14 patients among all the 21 patients. There were seven patients left in this group who need further evaluation.

In total, with the guidance of MII-pH monitoring, 64.1% (25/39) of refractory GERD patients accomplished symptom relief.

Conclusion

The mainstay therapy for GERD is PPI, which could block the end stage of gastric acid secretion. PIPs have been proved to be very effective in the GERD treatment. Through previous studies, it has been known that about 70% of patients with erosive esophagitis and 60% of patients with non-erosive reflux disease could obtain symptom relief after PPI therapy for more than 8 weeks. However, there are still some patients who suffer from persistent reflux symptom after PPI therapy, which is defined as refractory GERD. The cause of the refractory GERD has been studied using the combined MII-pH monitoring through which all categories of reflux could be detected. However, the management of refractory GERD remains unclarified even though the MII-pH monitoring could help find out the reason for persistent reflux symptoms. In the current study, the authors explored the cause of refractory GERD patients and tailored the subsequent therapy through the guidance of the MII-pH monitoring. It was indicated through the current study that the majority of the persistent reflux symptoms could attribute to the functional heartburn although the non-acid reflux contributed about 30.8% of the persistent symptoms. Through the tailored therapy, 64.1% of refractory patients obtained satisfactory symptom control.

Multichannel intraluminal impedance-pH has been utilized to detect all the possible reflux responsible for the persistent reflux symptoms. Through the impedance ring placed in the catheter, this device is able to detect all kinds of reflux including acid and non-acid, liquid, and gas reflux episodes. What is more, this technique makes the calculation of symptom association probability feasible. The study by Sharma et al. analyzed the possible reasons for PPI failure within 200 patients using the MII-pH monitoring. They confirmed the role of MII-pH monitoring in defining the causes for PPI failure, and they also speculated the importance of guiding
the subsequent therapy with this technique. The MII-pH was also advocated by Becker et al. in the guidance of management of refractory GERD. The way of grouping the refractory GERD patients varied through different studies. It has been suggested by Boeckxstaens et al. that four phenotypes of patients could be identified among refractory GERD patients after 24-h MII-pH monitoring and each with unique management consideration. The four phenotypes included excessive reflux and positive symptom association, physiological reflux and positive symptom association, excessive reflux and negative symptom association, and physiological reflux and negative symptom association. In the current study, the MII-pH monitoring helped define patients according to their reflux acidity, which differed from the previous suggested grouping rationale. This grouping was more practical when we tried to adjust the therapy according to the group.

On top of various reasons for persistent GERD symptoms, the non-acid reflux plays an important role. It was reported by Mainie et al. that non-acid reflux was responsible for persistent reflux symptoms among 37% of 168 GERD patients with PPI failure. A similar study by Zerbib et al. in France confirmed that 16.7% of persistent symptoms was non-acid reflux related, while only 5% was related to acid reflux. In the current study, the non-acid reflux contributed to 30.7% of all the persistent reflux symptoms. Thus, non-acid reflux is closely related to persistent reflux symptom. However, the pathogenesis of reflux symptom caused by non-acid reflux is unclear. The possible cause factors were bile acid and pepsin in the gastric juice. The speculated mechanism included the direct injury of bile acid and pepsin to the esophageal mucosa and subsequently caused the dilated intracellular space, which make the chemical receptor of pain exposed to the outer environment and activate the nocireceptor in the central nervous system.

The management of refractory GERD has been a clinical difficulty; there is no universal therapy for these patients due to the inconsistent causative factors of persistent symptoms. In this case, the “tailored therapy,” which aims to treat the different cause of persistent reflux symptoms according to the grouping of MII-pH monitoring, seems to be the best option. In the current tailored therapy, double dose of esomeprazole was given to those with acid overexposure to better control the esophageal and gastric acid. For the non-acid reflux, therapy target on the inhibition of transient LES relaxation has been proposed. However, the baclofen, which acts on the transient LES relaxations, was reported to have varieties of adverse effect including dizziness and vomit. Thus, we tried to treat these patients with double dose of esomeprazole considering that all the non-acid reflux was detected on PIP. It turned out that half of the patients with non-acid reflux obtained symptom relief, suggesting that enhancing the inhibition of gastric acid output might be helpful to those patients with non-acid reflux during MII-pH monitoring on PPI. This is a unique attempt in the treatment of non-acid reflux. The rationale for this attempt lied in the non-acid reflux (mostly weakly acidic reflux) could be transformed from the acid reflux after initial PPI therapy; the reinforced acid inhibition cleared the residual acid component. For patients with functional heartburn, the paroxetin resolved two-third of persistent symptoms. In total, the “tailored therapy” has improved the symptom resolution rate by 60.7%. A study by Becker et al. adjusted the therapy for persistent reflux symptom patients with the guidance of MII-pH monitoring; 90.9% of patients achieved symptom relief in the end. Thus, the MII-pH monitoring was a very useful tool to treat the refractory GERD, and “tailored therapy” would be a promising strategy in the management of refractory GERD.

There were some limitations in the current study. First, the sample size of the study was small, and a further study with a larger sample size would be helpful to clarify the management of refractory GERD. Second, only two treatment options were applied in the current study; more treatment options should suggest as tailored therapy in the clinical practice. However, the tailored therapy was a new attempt so far; too many treatment options might confound the outcome. More options could be attempted later.

In summary, acid overexposure, non-acid reflux, and functional heartburn were the most common reasons for persistent symptoms using the MII-pH monitoring. With the guidance of this technique, a tailored therapy could resolve the persistent reflux symptoms in among two third of patients.

Acknowledgements

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References

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