

# Clinical trial: persistent gastro-oesophageal reflux symptoms despite standard therapy with proton pump inhibitors – a follow-up study of intraluminal-impedance guided therapy

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## Publication data

Submitted 15 August 2007  
First decision 01 September 2007  
Resubmitted 12 September 2007  
Accepted 22 September 2007

## SUMMARY

### Background

Persistent gastro-oesophageal reflux disease (GERD), despite proton pump inhibitor (PPI) therapy, is a common problem. Combined pH/impedance monitoring (pH/MII) enables detection of reflux episodes.

### Aim

To identify patients with objective episodes of persistent reflux and second, to evaluate the effect of modified therapy based on the results of pH/MII.

### Methods

In all, 143 patients were examined with pH/MII because of GERD-symptoms resistant to PPI-therapy. Patients with pathological pH/MII (group 1) and with normal results (group 2) were identified. Therapy modifications were evaluated after a minimum follow-up of 3 months.

### Results

In 56 of 143 (39.1%) patients, pathological findings in pH/MII were identified. Therapy was escalated in 33/52 patients (group 1) and in 30/71 patients (group 2). Escalating therapy led to symptomatic relief in 90.9% of the patients in group 1 and 43.3% of the patients in group 2 ( $P < 0.001$ ).

### Conclusions

GERD symptoms refractory to PPI-therapy could be objectively identified with pH/MII in almost 40% of all patients. Furthermore, escalating anti-reflux therapy if pH/MII was pathological is associated with a significantly higher rate of successful treatment compared to the patients with normal findings. Therefore, pH/MII facilitates a more focussed therapeutical approach to patients with PPI-resistant GERD.

*Aliment Pharmacol Ther* 26, 1355–1360

## INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a recurrent disorder, which is increasing in frequency of its incidence.<sup>1</sup> Epidemiological studies indicate that approximately 40% of the western adult population occasionally suffers from one of the two predominant symptoms of GERD—heartburn or regurgitation. About 20% of the western population report GERD symptoms at least once weekly.<sup>2</sup> Proton pump inhibitors (PPIs) are effective, well tolerated, provide the best healing rates for acute oesophagitis and maintain remission better than H<sub>2</sub>-blockers.<sup>3</sup> In the majority of patients, PPI-therapy for 2–4 weeks leads to considerable relief of symptoms.<sup>4</sup>

However, approximately 20–40% of GERD-patients do not adequately respond to standard or even high-dose PPI therapy.<sup>4, 5</sup> These patients remain the most challenging problem in the management of GERD. In patients with persistent symptoms, it is often unclear whether symptoms are caused by inadequately treated GERD or other functional disorders. Treatment failure of GERD may result from an insufficient dose of PPI or rare disorders such as fast metabolizing patients.<sup>6</sup> In these patients, changing or escalating therapy could improve symptoms. However, escalating acid-suppressive therapy which is often used empirically in clinical practice would be of limited value in patients who are non-compliant or suffer from functional disorders.

Combined pH/impedance monitoring (pH/MII)-measurement offers a means of evaluating the quantity and quality of non-acidic and weakly acidic reflux episodes in the oesophagus.<sup>7–9</sup> This method has been shown to be highly sensitive for detecting all types of reflux episodes.<sup>10, 11</sup> Thus, pH/MII monitoring might be a promising tool to evaluate pathological reflux episodes in patients refractory to PPI therapy. However, to the best of our knowledge there are no follow-up data on pH/MII in a clinical setting evaluating patients with PPI-resistant GERD.

Therefore, the aim of our study was first to objectively identify patients with persistent pathological reflux episodes despite PPI-therapy and second, to evaluate the benefit and clinical relevance of modifying therapy according to the results of pH/MII monitoring.

## PATIENTS AND METHODS

### Patients

All patients who were evaluated with combined pH/MII between January 2005 and November 2006 for

persistent typical reflux symptoms (heartburn, regurgitation), despite standard PPI therapy for at least 1 month or more, were included. Endoscopy of the upper gastrointestinal-tract had been performed within the last 12 months or was performed before pH/MII measurement. Exclusion criteria were history of previous gastric or oesophageal surgery, severe oesophageal motility disorders or discontinuous PPI intake within the last 4 weeks before measurement. All patients completed a symptom-based questionnaire detailing typical reflux symptoms as well as age, gender, body-mass-index and consumption of nicotine and alcohol. In all patients, informed consent for data evaluation was obtained.

### pH/Impedance monitoring and data recording

Combined pH/MII monitoring was performed using an ambulatory, multi-channel, intra-luminal impedance system, consisting of a portable data logger and a combined pH-impedance catheter (Tecnomatix ZAN S 61 C 01 E, Sandhill Scientific, Highlands Ranch, CO, USA). Six impedance-electrodes as well as a distal pH-antimon probe were placed at pre-defined spots on this catheter (3.0 cm, 5.0 cm, 7.0 cm, 9.0 cm, 15.0 cm and 17.0 cm; pH-probe 5.0 cm). The catheter was placed with the pH antimon probe located 5-cm above the manometrically defined lower oesophagus sphincter. Data were recorded for at least 22 h. Stored data were then uploaded on a personal computer and analysed using a commercially available software system (BioView, Sandhill Scientific). Gastro-oesophageal reflux detected by impedance changes was defined on the basis of previous studies.<sup>12–14</sup>

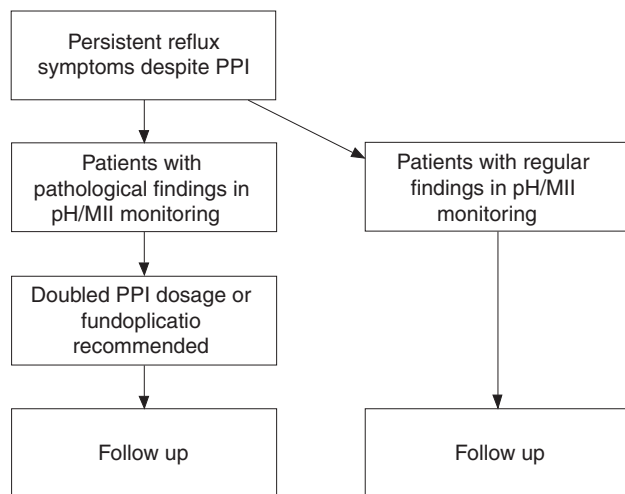
Reflux episodes were defined as either acidic or non-acidic, if a retrograde bolus movement was detected by impedance and pH value was below or above 4, respectively. Furthermore, the content of the reflux episode was characterized according to its composition (gas, fluid or mixed). Following the suggested reference values as published by Shay and Zerbib,<sup>13, 15</sup> MII was considered pathological when more than 73 fluid and/or mixed reflux episodes occurred in the oesophagus during 22–24 h. pH-monitoring of the oesophagus was considered pathological when the percentage of time the pH was below 4 was more than 4%. Meals were excluded from analysis. The patients were asked to indicate the predominant symptoms in the course of the measurements to assess symptom index (SI). SI was defined as the number of symptoms

associated with reflux divided by the total number of symptoms. SI was analysed using a commercially available software system (BioView, Sandhill Scientific) and was considered positive if more than 50% of the symptoms were associated with reflux. Symptoms were considered to be related to reflux if they occurred within 5 min of the onset of a reflux episode.

### Further treatment and follow-up of patients

Patients with pathological pH/MII results (group 1) and patients with normal results (group 2) were differentiated. After evaluating the pH/MII, patients with pathological findings (group 1) were advised to modify therapy by using high-dose PPI-therapy (doubling standard dosage) or to undergo fundoplication. This was individually discussed with the patients and did not depend on the pH/MII results. In contrast, no specific recommendations were made if no pathological findings were identified (group 2). In the latter group, further treatment was based on the individual decisions of the family doctors or the patients themselves (Figure 1).

Therapy modifications of high-dose PPI-therapy or fundoplication were evaluated after a minimum follow-up period of 3 months. All patients were interviewed regarding their actual symptoms and therapy using the same questionnaire as mentioned above.



**Figure 1.** Flow chart demonstrating the intended management of patients based on the results of pH/MII monitoring.

### Statistics

Data are shown in a descriptive manner. Differences between both groups were analysed by the Chi-squared test/Fisher's exact test, Student's *t*-test or Mann-Whitney-U test, as appropriate. A *P* value below 0.05 was regarded as statistically significant. For all calculations, SPSS for Windows 14.0 software package (SPSS, Chicago, IL, USA) was used.

## RESULTS

The study comprised 143 patients who met the inclusion criteria. Clinical examinations were well tolerated in all subjects and we did not experience any technical failures.

### Results of pH/MII monitoring and patient data

Pathological findings on pH/MII monitoring, despite ongoing PPI therapy were identified in 56 of 143 (39.1%) patients (group 1). Amongst these, six (4%) patients had pathological findings only on pH monitoring, 36 (25%) patients had pathological findings only on impedance measurement, 14 (10%) patients had a pathological result on both pH-metry and impedance monitoring. The remaining 87 (60.9%) patients had normal pH and MII results (group 2).

Obesity and the presence of hiatal hernias were the only factors significantly associated with pathological results on pH/MII monitoring. No significant differences could be assessed between group 1 and 2 for sex, age, endoscopic reflux oesophagitis or lifestyle factors such as consumption of alcohol and nicotine (Table 1).

### Symptom index

In the group of patients with pathological findings on pH/MII monitoring (group 1), 40 of the symptomatic subjects (78.4%) had a positive SI, 11 (21.5%) had a negative SI and five (8.9%) patients reported no symptoms during examination. In group 2, 18 (20.7%) patients had a positive SI, 63 (72.4%) a negative SI and six (6.9%) subjects reported no symptoms during examination. This difference between both groups (patients with and without pathological findings on pH/MII monitoring) was statistically significant ( $P < 0.001$ ).

	Patients with pathological findings	Patients with no pathological findings	<i>P</i>
Sex (male/female)	50%	55.2%	NS (Mann–Whitney)
Age (mean ± s.d.)	53.5 ± 14.2	56.2 ± 15.5	NS (T-Test)
BMI > 25 (%)	<b>62.5%</b>	35.6%	<b>0.002 (Chi square)</b>
Reflux oesophagitis (%)	21.6%	21.8%	NS (Mann–Whitney)
Hiatal hernia (%)	<b>58.5%</b>	39.8%	<b>0.036 (Chi square)</b>
Alcohol (%)	33.9%	40.2%	NS (Mann–Whitney)
Nicotine (%)	17.9%	13.8%	NS (Mann–Whitney)
Follow-up (median months)	7	6	NS (Mann–Whitney)

**Table 1.** Patient data and results (significant differences between patients with pathological or not pathological pH/MII are marked in bold)

### Results of further therapy and follow-up examination

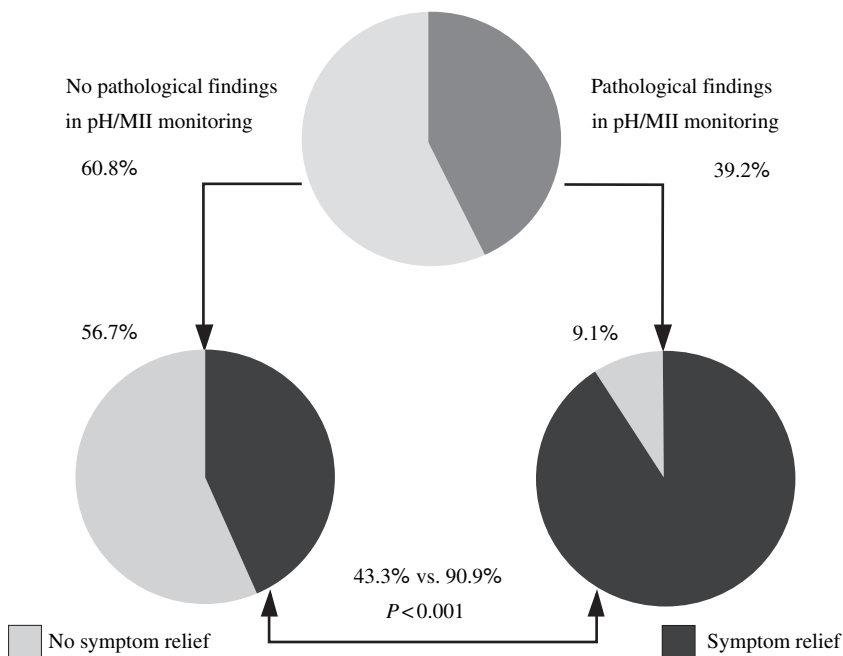
Follow-up data were available in 52/56 (92.9%) patients of group 1 (pathological findings on pH/MII). Amongst these, 4/52 (7.7%) patients underwent surgery. At follow-up examination, all operated patients reported significant symptom relief (100%). PPI therapy was escalated as recommended in 33/52 (63.5%) patients of whom 30/33 (90.9%) reported a significant symptom relief at follow-up (Figure 2). In this group, 29/33 (87.8%) patients had a positive SI.

Follow-up data were available in 71/87 (81.6%) patients of group 2 (no pathological findings in pH/MII). As mentioned before, no recommendations for further therapy were made if pH/MII was normal. However, at follow-up, 30/71 (42.3%) patients

reported having their PPI dosage increased based on the recommendations of their general practitioners or by themselves. However, in contrast with the 90.9% of patients in group 1, only 13/30 (43.3%) reported significant symptom relief after increasing the PPI-dosage. The difference between the two groups proved to be statistically significant ( $P < 0.001$ , Chi-squared test). Additionally, in group 2, only 1/30 (3.3%) patient had a positive SI.

### DISCUSSION

According to the results of our study, almost 40% of patients with GERD have measurable pathological reflux episodes despite standard PPI therapy. This reinforces findings based on previously published data showing that about one-third to one-half of patients



**Figure 2.** Symptom relief in patients with and without pathological findings in pH/MII monitoring: Significant difference between both groups after increasing the proton pump inhibitor-dosage ( $P < 0.001$ , Chi-squared test).

with PPI-resistant reflux symptoms has pathological findings, depending on the criteria used to define pathological results (positive SI in pH/MII or total number of reflux episodes).<sup>5,7</sup> Pathological findings were predominantly detected in patients with a body mass index (BMI) greater than 25 or with the presence of hiatal hernias. Previous studies have shown that increased BMI is a risk factor for GERD.<sup>16</sup> This might be because of extrinsic gastric compression by surrounding adipose tissue leading to an increased intra-gastric pressure and impaired gastric emptying with subsequent relaxation of the lower oesophageal sphincter.<sup>6,17-19</sup> Obese patients may also have an increased risk for hiatal hernia, which might play a role in initiating and promoting GERD.<sup>20</sup>

For assessing the role of pH/MII monitoring in detecting reflux in our population, the issue to be determined is as to which parameters are best suited. In the current study, we focussed on the total number of reflux episodes and the relative acid reflux time determined by pH-monitoring. The reason for this approach is that the number of reflux episodes can be assessed in a standardized fashion with available reference values.<sup>14,15</sup> We used the commonly employed number of 73 fluid and/or mixed reflux episodes within 22–24 h. Although, these values were generated in patients off PPI therapy, the reason for using these reference values is the fact that there are no common reference values for patients on PPI, so far. We therefore considered that this conservative approach (i.e. using reference values acquired from patients off PPI) is best suited to generate reliable data.

One might argue that the use of SI and/or symptom association probability is adequate to determine the need for escalation of therapy. However, the aims of the present study were to objectively identify patients with persistent pathological reflux episodes despite PPI-therapy and secondly to adapt further therapy according to the objective results of pH/MII monitoring. Hence, the reliance on a symptom association analysis is too vague and subjective to answer our questions. Nevertheless, as shown, there was good agreement between SI and total number of reflux events. This demonstrates that both objective and subjective findings are related to each other.

Of interest was the finding that patients with pathological findings on pH/MII did benefit to a greater

extent from escalating therapy compared to patients with a normal pH/MII. This might be related to the fact that further inhibition of acid can lead to a decrease in gastric volume and gastric distension resulting in fewer transient lower oesophageal sphincter relaxations and thereby improvement of reflux symptoms.<sup>8</sup> We were also able to show in a limited number of patients that surgical laparoscopic fundoplication is beneficial in patients with persistent symptoms, despite being on PPI, and abnormal pH/MII monitoring. This corresponds with previous results by Maine *et al.*<sup>21</sup> Hence, the decision to perform fundoplication in PPI-resistant GERD patients might be facilitated and the potential risk to over-treat these patients by surgery can be reduced.

By contrast, in the group with regular results on pH/MII monitoring there was a significant minor symptom relief after escalation of therapy. In most of the patients in this category, persistent gastro-oesophageal reflux as a cause of symptoms appears unlikely. Increasing the PPI dose is, therefore, of limited value and treatment of functional disorders should be considered.

In conclusion, combined 24 h-pH/impedance measurement identifies pathological gastro-oesophageal reflux episodes in almost 40% of symptomatic patients despite ongoing PPI therapy in standard dosage. Furthermore, escalating anti-reflux therapy is associated with a significantly higher success rate if pH/MII was pathological. Thereby, pH/MII enables a tailored therapeutic approach to patients with PPI-resistant GERD and ensures the success of further therapy (escalation of the PPI-dose, surgery). Treating patients on the basis of pH/MII results rather than treating them empirically will result in cost savings as well as increased treatment success. This approach complies with the challenging demand for patient-friendly and cost-effective management of GERD in daily practice.

## ACKNOWLEDGEMENTS

We thank Barbara Heartwell, BSc, MD, FRCS(C), Adjunct Professor, Department of Surgery, University of Western Ontario, Windsor, Ontario, for valuable discussion and help. *Declaration of personal and funding interests:* None.

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