

# Patients with refractory reflux symptoms often do not have GERD

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## Key Messages

- The aim of this study is to determine the underlying cause of reflux symptoms refractory to PPI therapy in tertiary referral patients.
- All patients with reflux symptoms not responding to PPI therapy, who underwent diagnostic testing with 24-h pH-impedance monitoring and gastroscopy, were analyzed.
- Sixty-nine patients (65.1%) ended up with a final diagnosis of GERD while 32 patients (30.2%) were diagnosed with functional heartburn.
- Epigastric pain and a secondary diagnosis of functional dyspepsia could be associated with a final diagnosis of functional heartburn.
- Approximately one-third of the patients referred with refractory reflux symptoms do not have GERD, but instead have other disorders, predominantly functional heartburn, which require a different therapeutic approach.

## Abstract

**Background** In patients with typical reflux symptoms that persist despite proton pump inhibitors (PPIs) it is sometimes overlooked that treatment fails due to the presence of other disorders than gastroesophageal reflux disease (GERD). The aim of this study was to determine the underlying cause of reflux symptoms not responding to PPI therapy in tertiary referral patients. **Methods** Patients with reflux symptoms refractory to PPI therapy who underwent 24-h pH-impedance monitoring were analyzed. Patients in whom a diagnosis was already established before referral, who had previous esophageal or gastric surgery, or who had abnormalities on gastroscopy other than hiatus hernia, were excluded. **Key Results** In total, 106 patients were included. Esophageal manom-

etry showed achalasia in two patients and distal esophageal spasm in another two. Twenty-four-hour pH-impedance monitoring revealed a total acid exposure time <6% in 60 patients (56.6%) of which 25 had a positive symptom association probability (SAP) while 35 showed a negative SAP. Sixty-nine patients ended up with a final diagnosis of GERD while 32 patients (30.2%) were diagnosed with functional heartburn (FH), two with functional chest pain, two with achalasia, and one with rumination. A trend toward an association with a final diagnosis of FH was found with the atypical symptom epigastric pain ( $p = 0.059$ ) and with a secondary diagnosis of functional dyspepsia ( $p = 0.083$ ). **Conclusions & Inferences** Approximately one-third of the patients referred with refractory reflux symptoms suffer from disorders other than GERD, predominantly FH. This explains, at least partly, why many patients will not benefit from acid inhibitory treatment.

**Keywords** functional heartburn, PPI, refractory reflux symptoms, treatment failure, unresponsive.

**Abbreviations:** FH, functional heartburn; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LES, lower esophageal sphincter; NERD,

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non-erosive reflux disease; PPI, proton pump inhibitor; SAP, symptom association probability.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is caused by the reflux of gastric contents into the esophagus and is one of the most prevalent chronic diseases, affecting up to 27.8% in North America and up to 25.9% in Europe.<sup>1</sup> Proton pump inhibitors (PPIs) represent the main treatment due to its remarkable efficacy in both the healing of erosive esophagitis and symptom relief.<sup>2,3</sup> However, several studies have shown that the use of the standard PPI dose once daily results in either a partial or complete lack of response of symptoms in up to 40% of GERD patients after a 4-week course.<sup>4,5</sup> As a result, the most frequent presentation of GERD patients in tertiary referral gastrointestinal practices has become refractory symptoms to PPIs.<sup>6</sup> As refractory GERD is not only associated with a significant decrease in all the mental and physical domains of health-related quality of life questionnaires,<sup>7</sup> but also with a significant increase in current healthcare costs,<sup>4,5</sup> its management has become a very challenging and important task.

Gastroesophageal reflux disease is associated with a large range of symptoms, which can be split into the typical and the atypical reflux symptoms. Typical symptoms consist of heartburn and acid regurgitation, while atypical symptoms are more diverse and consist of non-cardiac chest pain, chronic cough, hoarseness, globus, and throat irritation.<sup>8</sup> Endoscopy is used to distinguish patients with reflux esophagitis and/or Barrett's esophagus from patients without macroscopic mucosal damage. The latter is the category of non-erosive reflux disease (NERD) patients. However, it is important to note that the diagnosis of NERD can only be established when in addition to the absence of abnormalities during upper endoscopy there is objective evidence that reflux is the cause of the patients' symptoms (i.e. by 24-h pH or pH-impedance monitoring). In patients with functional heartburn (FH) there is no relation between symptoms and reflux. According to the Rome III-criteria for functional gastrointestinal disorders, the diagnosis of FH is made when there are no indications that reflux is the cause of the patients' heartburn (no erosions during endoscopy, normal acid exposure, no response to acid suppression, and a negative symptom-reflux association (i.e. symptom association probability [SAP] <95%).<sup>9,10</sup>

It has been demonstrated that the lowest rates of response to PPIs are seen in patients with normal acid

exposure and a negative symptom-reflux association.<sup>11</sup> Thus, it is important to consider the presence of a functional disorder when patients have refractory GERD symptoms. As FH demands a different treatment than GERD, it is crucial to distinguish these patients from GERD patients.

The aim of this study is to determine the underlying cause of reflux symptoms not responding to PPI therapy in tertiary referral patients. The hypothesis is that PPI non-responders referred to a specialist often have a functional disorder and therefore do not respond to acid suppressant therapy.

## MATERIAL AND METHODS

### Patients

All patients referred to our center from 04-2011 until 01-2015 for analysis of reflux symptoms refractory to PPI therapy who underwent diagnostic testing with 24-h pH-impedance monitoring were retrospectively analyzed. All patients were required to have at least one typical symptom (heartburn, regurgitation, or retrosternal pain), be 18 years of age or older, and either have had a gastroscopy before or after referral. If eosinophilic esophagitis was suspected, this was ruled out. Patients in whom a diagnosis with explanation of their symptoms was already established before referral, for example with pH-impedance monitoring, who had previous esophageal or gastric surgery, or who had signs of esophagitis or Barrett's esophagus on gastroscopy, were excluded. Moreover, patients with a history of serious motility disorders such as achalasia or spasms were also excluded. The study proposal was submitted to the local institutional review board of the academic medical center in Amsterdam, the Netherlands, and formal evaluation was waived (reference number W15\_049 # 15.0060).

### Stationary conventional esophageal manometry

Esophageal manometry was carried out prior to the 24-h ambulatory pH-impedance study according to the routine protocol used in our institution. A 10-channel water-perfused multilumen silicon rubber manometric catheter with in-built sleeve sensor (Dentsleeve Int, Mississauga, ON, Canada) was passed transnasally and the patient was placed in the supine position. The catheter was perfused at a rate of 0.15 mL/min with degassed water. A slow pull-through technique was used to determine the position of the lower esophageal sphincter (LES). Following this, the sleeve sensor was positioned across the gastroesophageal junction. Pressure was recorded with side-holes in the stomach, at the proximal margin of the sleeve, and at 3, 6, 9, 12, 15, 18 and 26 cm above the LES. The esophageal motility was measured using 10 consecutive water swallows of 5 mL. Dedicated data analysis software was used to analyze and store the data (MMS, Enschede, The Netherlands). The manometric anomalies were defined according to Spechler and Castell.<sup>12</sup>

### Ambulatory pH-impedance monitoring

All subjects underwent 24-h esophageal pH-impedance monitoring off acid suppressive therapy. Patients were instructed to

discontinue PPIs for at least 7 days, and H2RAs, prokinetic agents and antacids for at least 3 days prior to the study. This ambulatory measurement was carried out according to the routine protocol used in our institution. A combined pH-impedance catheter was inserted into the esophagus through the patient's nose. The catheter contained six impedance segments and one ion-sensitive field-effect transistor pH electrode (Unisensor AG, Attikon, Switzerland) for pH monitoring. The latter was placed with the pH electrode 5 cm above the manometrically localized LES. The impedance recording segments were located at 2–4, 4–6, 6–8, 8–10, 14–16, and 16–18 cm above the upper border of the LES. Both the impedance and pH measurements were stored on a digital datalogger (Ohmega, Medical Measurement Systems [MMS], Enschede, The Netherlands), using a sampling frequency of 50 Hz.

Patients were instructed to restrict their intake to three meals and four beverages at standardized times throughout the 24 h. Patients were told to consume their meals and drinks within 30 and 15 min, respectively, and mark these times down in the diary. They were also encouraged to maintain their normal daily activities throughout the measurement. Clear instructions were given on how to promptly activate the event marker button on the pH datalogger whenever they experienced symptoms after which they should write the symptom and time down in the diary. Moreover, patients were instructed to mark the period spent in the supine position.

## Outcome evaluation

Patient outcome data were obtained by reviewing hospital files regarding consultations after measurements and/or by telephone interview. Patients were asked about the type of treatment and dosage, and whether they had symptom relief of >50%.

## Data analysis

For each patient the acid exposure time was calculated. This was defined as the total percentage of time in which the pH in the distal esophagus was <4. Values  $\geq 6\%$  were considered to be pathological according to previously described criteria.<sup>13</sup> Symptoms, associated symptoms, the number of reflux episodes and the SAP were recorded. A symptom was considered to be associated to a reflux episode if this was perceived within 2 min following the initiation of the reflux. For calculation of the SAP, the measurement is divided into 2-min intervals after which the presence or absence of reflux events and symptoms during each 2-min interval is determined.<sup>9</sup> A two-tailed Fisher's exact test is then used. A SAP  $\geq 95\%$  suggests an association between symptoms and reflux events and was interpreted as a positive SAP.

The chi-squared test was used to calculate the association between FH and epigastric pain, a secondary diagnosis of functional dyspepsia, and the absence of a hiatus hernia. The association between hiatus hernia and a final diagnosis of GERD, and between hypersensitive esophagus and epigastric pain was also calculated.

## RESULTS

Between January 2011 and January 2015, 106 patients (61 females, median age 49), who were unresponsive to PPI treatment, were included. All patients had at least one typical GERD symptom and underwent a 24 h pH-impedance measurement after cessation of acid sup-

pressive therapy. In all patients esophagitis and Barrett's esophagus were ruled out with gastroscopy. None of these patients had a history of serious motility disorders or previous esophageal or gastric surgery.

Table 1 gives an overview of the frequency of each symptom reported during the study. The majority of the patients (94.3%) reported more than one reflux symptom.

## Stationary conventional esophageal manometry

In 104 patients (98.1%) the 24-h pH-impedance monitoring was preceded by esophageal manometry. In 24 patients (22.6%) minor motility defects were found with the most prevalent being an ineffective motility. More importantly, seven patients (6.6%) had serious motility disorders, with two patients having a diagnosis of achalasia, two patients with aperistalsis, two with distal esophageal spasm, and one with a nutcracker esophagus.

## Ambulatory pH-impedance monitoring

In all patients 24-h pH-impedance monitoring was performed successfully. A total acid exposure time more than 6% was found in 46 patients (43.4%). Of the 60 patients (56.6%) with an exposure time less than 6%, 25 (23.6%) had a positive SAP while 35 patients (33.0%) showed a negative SAP.

## Diagnosis

Fig. 1 gives an overview of the primary diagnoses made in the study. As a result of the investigations, the majority of the patients (65.1%) ended up with a final diagnosis of GERD, while 32 patients (30.2%) were diagnosed with FH. Impedance monitoring resulted in four patients being diagnosed as GERD instead of FH as

**Table 1** Demographics and clinical characteristics

Characteristic	
Total patients	106
Median age (years)	49
Female gender	61 (57.5%)
Typical symptoms	
Heartburn	96 (90.6%)
Regurgitation	71 (67.0%)
Retrosternal pain	42 (39.6%)
Atypical symptoms	
Epigastric pain	45 (42.4%)
Belching	27 (25.5%)
Dysphagia	24 (22.6%)
Globus	13 (12.3%)
Hoarseness	8 (7.5%)
Cough	5 (4.7%)

they only had a positive SAP when taking weakly acidic and alkaline reflux episodes into account. Two patients were diagnosed with functional chest pain, two with achalasia and one with rumination. A secondary diagnosis was present in 11 patients, which included functional dyspepsia ( $n = 9$ ) and esophageal spasm ( $n = 2$ ). There was a trend toward an association between the diagnoses functional dyspepsia and FH (Chi-square test with  $p = 0.083$ ).

Epigastric pain (42.4%), which was the most frequent atypical symptom mentioned, trended toward an association with a final diagnosis of FH ( $p = 0.059$ ), but not toward an association with hypersensitive esophagus (physiological acid exposure in combination with a positive SAP;  $p = 0.86$ ).

A hiatus hernia was present in 46 patients (43.4%). The absence of a hiatus hernia was not associated with the diagnosis of FH ( $p = 0.22$ ), but the presence of a hiatus hernia trended toward an association with a final diagnosis of GERD ( $p = 0.095$ ).

## Outcome

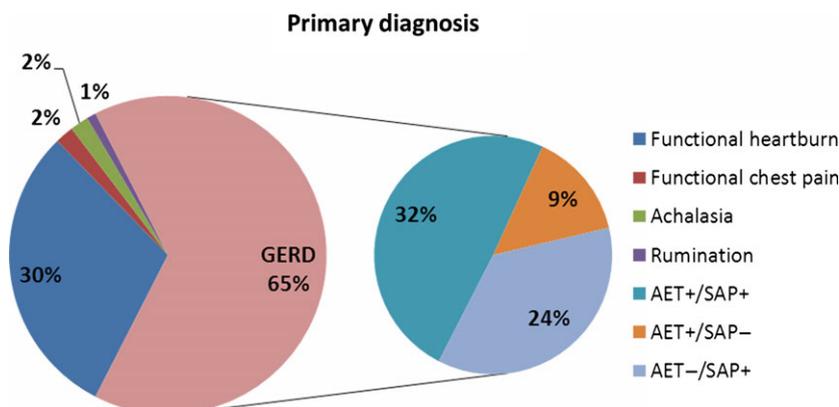
Sixteen patients were lost to follow-up, of which nine patients with GERD, five with FH, one with functional chest pain and the patient with rumination. Of the 27 patients with FH who were included in follow-up, only eight patients attempted using amitriptyline as treatment. Fifty percent of these patients had a beneficial effect (>50% symptom relief). Sixty patients with a primary diagnosis of GERD were included in follow-up, of which 76.7% had a beneficial effect to treatment. In the subgroup of patients with a hypersensitive esophagus (an acid exposure time <6% and a positive SAP), eight patients used amitriptyline of which 75% had a beneficial effect. The other 13 patients in this subgroup used PPIs, with 53.8% having a beneficial effect. Of the other 39 GERD patients included in follow-up, with an acid exposure time  $\geq 6\%$ , eight patients had a Nissen

Fundoplication with all a great result, and 27 patients used PPIs with 77.8% having symptom relief of >50%.

## DISCUSSION

In tertiary referral gastrointestinal practices reflux symptoms refractory to PPIs has become one of the major predicaments. Reflux-related symptoms are considered refractory when the use of PPI treatment for 12 weeks or more causes an improvement of symptoms of <50%.<sup>14</sup> It is now understood that multiple underlying mechanisms are involved in PPI failure in GERD patients. Using combined esophageal pH-impedance monitoring it has been shown that refractory symptoms are often associated with weakly acidic reflux events<sup>15,16</sup> and that reflux events with high proximal extent are more frequently symptomatic in patients off<sup>3,17</sup> and on<sup>3,18,19</sup> PPI therapy. Moreover, several mechanisms such as visceral hypersensitivity have been suggested to contribute to symptom perception<sup>20</sup> and thus to PPI-resistant symptoms in these patients. Multiple studies have demonstrated that *in vivo* and *in vitro* mucosal exposure to acid impairs the barrier properties.<sup>21–23</sup> It is hypothesized that this impairment of the esophageal barrier allows acid or other noxious components to stimulate submucosal nociceptors and thus provoke symptoms<sup>24</sup> and therefore have a key role in the pathophysiology of NERD.<sup>25</sup>

One of the dilemmas concerning NERD is the lack of a standard definition, which affects the results of clinical trials and makes the interpretation of data challenging. Many studies define NERD as the condition in which the patient has reflux symptoms but a negative gastroscopy. However, not all reflux symptoms are due to reflux and it is of significant importance to distinguish 'true' NERD patients from patients who have FH. Studies have demonstrated that the response to PPIs differs between different categories of GERD. Non-erosive reflux disease has been



**Figure 1** Primary diagnoses in patients with reflux symptoms refractory to PPI therapy after investigation with esophageal manometry and 24-h pH-impedance monitoring (shown as percentages). The GERD group is split into categories using acid exposure time  $\geq 6\%$  (AET+), acid exposure time <6% (AET-), symptom association probability  $\geq 95\%$  (SAP+), and symptom association probability <95% (SAP-).

clearly associated with more refractory symptoms in several studies in comparison to patients with erosive esophagitis.<sup>26,27</sup> However, these studies did not conduct pH-impedance measurements and thus did not distinguish the NERD patients from the patients with FH. This failure to separate FH from NERD could thus contribute in large measure to the therapeutic disappointment in GERD. This is supported by a meta-analysis which demonstrated that the previously reported low response rate in NERD patients is likely due to the inclusion of symptomatic patients who do not have GERD.<sup>28</sup> It is also interesting to note that patients who were diagnosed with GERD in this study due to a positive SAP, would have been classified as FH in the previous Rome-II criteria.<sup>29</sup> Thus, if the Rome-II criteria would have been used instead of the Rome-III criteria, a much larger proportion of the patients would have ended with a diagnosis of FH. One study researching the presence of FH in patients with GERD symptoms and a negative gastroscopy showed that 24% had FH, based on a negative total acid exposure time and a negative SAP.<sup>30</sup> This is of great importance as these patients benefit more from a different therapeutic approach. The use of visceral pain modulators, such as tricyclic antidepressants, is generally accepted as treatment for patients with FH, even though the clinical trials to support this are currently lacking.

Our study supports the importance of distinguishing the NERD patients from the patients with FH as we demonstrate that, using pH-impedance monitoring, approximately a third of the patients with a negative gastroscopy have a diagnosis of FH (30.2%) or functional chest pain (1.9%). Moreover, we demonstrate the importance of esophageal manometry in patients with refractory symptoms as two patients had a primary diagnosis of achalasia and one patient had rumination syndrome. These patients do not have GERD and would certainly not benefit from the typical approach of dose escalation or surgery but require a different treatment. This is of significant importance as surgery is not without risk. Our study thus provides evidence that further investigations, using pH-impedance monitoring and esophageal manometry, is beneficial in patients with refractory GERD symptoms as results could alter the therapeutic approach significantly.

Moreover, many studies looking into GERD symptoms refractory to PPI treatment require the symptom heartburn to be present. However, it has been demonstrated that the symptom regurgitation tends to be less responsive to acid suppression than heartburn in patients with GERD,<sup>31</sup> and in most GERD patients symptoms are not restricted to one certain domain of

GERD, but consist of a combination of various typical and atypical symptoms.<sup>32</sup> For this reason we have included all patients with at least one typical GERD symptom and not merely the patients with heartburn. Furthermore, studies have demonstrated that patients with a hypersensitive esophagus<sup>33</sup> (a normal esophageal acid exposure and a positive symptom association), but also patients with FH,<sup>34</sup> often have an overlap with dyspeptic symptoms. This is in part supported by our study as we found a trend toward an association between epigastric pain and FH ( $p = 0.059$ ) but not with hypersensitive esophagus ( $p = 0.86$ ). It has also been demonstrated that functional dyspepsia is associated with an absence of response to PPI treatment.<sup>3</sup> In our study, nine patients (8.5%) had a secondary diagnosis of functional dyspepsia, which had a trend toward an association with patients with FH ( $p = 0.083$ ).

Wireless pH-monitoring lasting 48 h or longer has been shown to increase the ability to record pathological reflux and to establish an association between symptoms and reflux,<sup>35-37</sup> yet this is based on the normative values used during 24-h measurements. Impedance measurement allows for the detection of weakly acidic and alkaline reflux episodes, which can still result in symptom perception. In our study, without impedance measurement, four patients would have been diagnosed with FH instead of hypersensitive esophagus as they only had a positive SAP when taking weakly acidic and alkaline reflux episodes into account. As both methods have advantages and disadvantages, it remains unclear which method is superior. Furthermore, it has been demonstrated that the use of 24-h pH-impedance monitoring is highly reproducible in GERD patients, and that this is also the case with measurement of SAP.<sup>38</sup>

A limitation of this study is that the data were collected retrospectively out of patient files. Strict inclusion criteria were maintained for patient selection, however, a retrospective study remains more susceptible to selection compared to a prospective study. The results on outcome should thus be considered with caution. In our study, conventional manometry was used in comparison to high-resolution manometry (HRM). However, the added value of HRM vs sleeve sensor manometry in diagnostic yield is probably not very large and the chance that significant diagnoses have been missed is small. The most important data in this aspect comes from Clouse *et al.* who demonstrated that topographical methods mainly have a benefit over pull through manometry in patients with achalasia and in segregating aperistaltic disorders.<sup>39</sup> That study was, however, conducted using a manometry system without a sleeve sensor, while in

our study we used a manometry system with sleeve, allowing for a better measurement of LES dysrelaxation which made the probability of missing achalasia very small.

In conclusion, approximately one-third of the patients referred with refractory reflux symptoms do not have GERD but instead suffer from other disorders, predominantly FH but sometimes rumination syndrome or achalasia. It is thus important to realize that the presence of refractory reflux symptoms does not equate to refractory GERD, and that this explains, at least in part, why many patients will not benefit from acid inhibitory treatment.

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## CONFLICTS OF INTEREST

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## AUTHOR CONTRIBUTION

TH collected data, analyzed and interpreted data, drafted the manuscript, critically revised the article for important intellectual content, and approved the final submitted draft; MT designed the study, collected data, analyzed and interpreted data, and approved the final submitted draft; PW designed the study and approved the final submitted draft; AB and AS designed the study, critically revised the manuscript for important intellectual content, and approved the final submitted draft.

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