Annals of Gastroenterology (2013) **26,** 6-10

Patients with refractory gastroesophageal reflux disease: diagnostic tools

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Abstract

Patients with refractory to proton pump inhibitors (PPIs) gastroesophageal reflux disease (GERD) symptoms are approximately 40% and represent a very common problem in clinical practice. Many of these patients do not have GERD, but suffer from functional heartburn or hypersensitive esophagus. After thorough clinical evaluation and failure of escalation of PPI dose, diagnostic investigations include endoscopy, esophageal manometry, pH testing, esophageal Bilitec and esophageal impedance with pH monitoring.

Keywords Refractory GERD, diagnosis

Ann Gastroenterol 2013; 26 (1): 6-10

Introduction

Refractory gastroesophageal reflux disease (GERD) can be defined as the presence of typical reflux symptoms that do not respond to therapy with acid-suppressing medications. Patients with symptoms who do not respond to proton pump inhibitors (PPIs) are increasingly seen in outpatient gastroenterology practice. It has been estimated that up to 40% of patients with GERD showed lack of symptomatic response to a standard (once a day) dose of PPI, either partially or completely [1-3]. Commonly, PPI dose escalation is the next therapeutic approach in non-responding GERD patients. However, the majority of patients will continue to experience GERD symptoms on these higher doses of PPIs [4].

Although there is an increase by almost 50% in the use of at least a double (twice daily) dose of PPIs, only 58% of those receiving PPIs report a high level of satisfaction with their treatment [3,5]. With the widespread use of multiple (once or twice daily) dose PPIs, the dosing and timing of PPI therapies to define treatment failure remains an area of controversy. Keeping in mind the fact that in almost all countries reimbursement for PPI use in patients with GERD is only for once a day, many investigators suggest that because of the lack of satisfactory symptomatic response this dose is sufficient to consider patients as PPI failures [6]. However, in a recent review refractory GERD was defined as <50% improvement in the chief complaint after at least 12 weeks of double dose PPI therapy [7]. The symptom burden should impair quality of life and symptoms must be "reflux-related".

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Conflict of Interest: None

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Received 4 July; accepted 24 July 2012

Diagnostic evaluation

The different proposed underlying mechanisms for refractory GERD include: poor compliance, weakly acidic reflux, bile reflux, visceral hypersensitivity (functional heartburn), nocturnal reflux, eosinophilic esophagitis, delayed gastric emptying, and others. Weakly acidic or bile reflux and visceral hypersensitivity are the most thoroughly studied mechanisms.

In a patient who fails to respond symptomatically to PPIs we should first determine whether the initial diagnosis of GERD is certain. There are various diagnostic options for patients with refractory GERD, although some of them appear to have a very low clinical value and are still limited to a few centers.

Symptom evaluation

Clarification of the actual nature of the persisting symptoms is crucial. Many patients are referred for refractory heartburn which appeared to be, after a careful interview, either epigastric burning or sore throat. In these patients, the probability of GERD-related persisting symptoms is lower compared to patients with typical heartburn [8].

Many patients with reflux symptoms showed adequate relief of heartburn with PPI therapy, whereas efficacy of PPI therapy for relief of regurgitation is considerably lower [9]. For many patients with refractory to therapy symptoms,

regurgitation is unbearable and these patients are probably good candidates for antireflux surgery.

The presence of functional disorders should be carefully assessed, as functional dyspepsia and irritable bowel syndrome are strongly associated with PPI failure in patients with abnormal reflux with pH-impedance monitoring [10]. The presence of psychological disorders should also be assessed in patients with refractory reflux symptoms, as high levels of anxiety were associated with persistent symptoms [11]. However, the possibility that refractory symptoms could be the cause and not the result of anxiety cannot be ruled out [12].

Checking for compliance and dosing time is important before embarking on additional investigations. Compliance to once daily PPI has been reported to be lower in patients with persistent symptoms (45-55%) compared to those with adequate relief (85%) [13].

Upper endoscopy - Esophageal histology

In clinical practice, upper endoscopy is the first tool used for evaluation of patients with lack of response to PPIs due to its availability. However, the value of gastroscopy has been shown to be very low, as the main source for refractory to PPIs GERD patients originate from the groups of patients with non-erosive reflux disease (NERD) and functional heartburn [14]. Keeping in mind that the healing rates of erosive esophagitis with PPIs once a day range from 75-95% and that endoscopic healing is not always accompanied with symptom relief, upper endoscopy is still helpful [6]. The hope is to identify anatomical abnormalities that can explain the treatment failure. Thus, the presence of mucosal injury despite PPIs treatment could be an indicator of poor compliance or partially healed erosive esophagitis. A recent study evaluating endoscopic findings in patients with persistent GERD symptoms *vs.* patients with heartburn who had not received PPIs challenged the utility of endoscopy in the refractory GERD group [15]. Anatomical findings during upper endoscopy were significantly more common in the no-treatment group compared with the refractory GERD group.

In contrast, in rare cases, endoscopy can reveal the presence of other disorders that could explain persistence of symptoms, such as pill-induced esophagitis, infectious esophagitis, and persistent peptic ulcer [14]. Further work-up should include histological examination of esophageal biopsies in order to identify presence of eosinophilic esophagitis, although its prevalence would not exceed 0.9-4% of patients with refractory GERD [8].

Moreover, esophageal histology can reveal the presence of dilated intercellular spaces (DIS) which has been proposed as a potential mechanism for symptoms in GERD [16-18]. In the esophageal mucosa DIS can be identified in virtually all GERD patients. The presence of DIS is likely to promote higher activation of sensory nerve endings which subsequently provoke symptom generation in patients with NERD [19]. Studies have shown that PPI treatment normalize DIS and resolve symptoms [20,21]. In contrast, DIS were still increased in refractory heartburn patients despite double PPI dose [22]. An experimental study showed that not only acidic but weakly acidic solutions containing bile acids could also provoke increased DIS [23]. Weakly acidic reflux is the predominant type of reflux in NERD patients on PPIs and it has been proposed that this type of reflux may be responsible for maintenance of symptoms in refractory to PPIs NERD patients. However, a recent study demonstrating the appearance of DIS in the exposed and non-exposed to reflux esophageal mucosa showed that induction of DIS may not coincide with reports of heartburn [24].

Even if conventional endoscopy is normal, minimal changes in the distal esophagus related to GERD could be detected by using novel endoscopic imaging techniques such as magnification endoscopy, chromoendoscopy, narrow band imaging (NBI) and confocal laser endomicroscopy (CLE) in patients with NERD. Magnification endoscopy alone or in combination with chromoendoscopy offers the chance for an improved detection of subtle findings in NERD, such as punctuate erythema above the Z-line, pinpoint vessels and triangular indentations. NBI and endomicroscopy are fascinating new tools, but they are time-consuming and access to these novel modalities in clinical practice is limited [25].

Esophageal manometry

All patients with refractory reflux symptoms should have esophageal manometry before reflux monitoring to position pH sensors and to rule out achalasia or severe esophageal motor disorders. The prevalence of heartburn has been reported to be as high as 35% in achalasia [14].

Esophageal pH monitoring

One of the most common uses of pH monitoring is in the evaluation of patients with persistent symptoms of GERD despite treatment. Both catheter and wireless esophageal pH testing could be performed; off PPIs to confirm if symptoms are truly the results of reflux or on PPIs to investigate whether the symptoms are due to persistently abnormal esophageal acid exposure [26].

In patients with refractory reflux symptoms, pH monitoring is most commonly done with the patient taking PPI therapy, usually at double dosing. In these patients, experts suggest a stricter definition of normal esophageal acid exposure with a cut-off of 1.6% for esophageal pH<4 [27]. Inclusion of a symptom-reflux correlation, such as symptom index (SI) and symptom association probability (SAP) helps to identify symptoms associated with acid reflux regardless of total esophageal acid exposure. However, the clinical accuracy of these indices remains a matter of debate. The agreement between SI and SAP is poor and for now it cannot be stated which test should be used in clinical practice [7]. A recent study showed that both indices were largely determined by chance occurrences unless patients with persistent to PPI therapy symptoms have high rates of reflux [28]. Although the study challenged the utility of SI and SAP, reflux association is clinically helpful to better identify patients with refractory to treatment symptoms [7].

A positive study suggests that persistent symptoms are due to insufficient acid inhibition. The likelihood of having abnormal pH study on PPI treatment varies among different PPI doses. On once daily dose 31% of refractory patients had abnormal test, compared to only 4% of patients on double omeprazole dose; 7% of patients with typical and 1% of patients with atypical reflux symptoms [29]. Another study reported that 16% and 32% of symptomatic patients on PPI twice daily and PPI once daily, respectively had an abnormal pH test [30]. Although the diagnostic yield of on-therapy pH monitoring for refractory patients is low, its clinical utility could be justified by the fact of identification of truly refractory GERD patients who may benefit from additional therapy.

A negative study (normal esophageal acid exposure and negative symptom-reflux correlation) after a trial of drug therapy provides convincing evidence that the patient's symptoms are not related to residual acid reflux. In cases of normal esophageal acid exposure and a positive symptom-reflux correlation, the possibility of esophageal acid hypersensitivity should be considered. A negative pH study on-therapy does not exclude the possibility of underlying reflux that may be a cofactor in a patient's presentation and is being adequately suppressed on PPIs [6,26].

The use of the wireless pH system allows pH testing both off and on PPIs in a single test [31]. By combining pH monitoring both off and on therapy, two questions can be answered: 1) does the patient have abnormal esophageal acid exposure consistent with GERD?; and 2) whether reflux is present, is it being suppressed by PPI therapy? [26]. Moreover, the prolonged recording time might also increase the likelihood of detection symptoms that are clearly correlated with acid reflux events [32]. However, a recent study questioned the value of extended pH monitoring, as 67% of refractory GERD patients had normal pH testing on both days of the study [33].

Esophageal Bilitec

Studies have demonstrated that combined acid and bile reflux was the most common reflux pattern in patients with GERD and presence of bile acid increased across the spectrum of GERD from 50% in patients with NERD to 95% in patients with Barrett's esophagus [34,35]. The Bilitec 2000, a fiberoptic spectrophotometric probe, was developed to quantify in an ambulatory fashion bile reflux by using bilirubin as a surrogate marker. Validation studies confirmed a good correlation between Bilitec measurements and bile acid concentrations [36,37].

Several studies showed that PPI administration reduced the occurrence of both acid as well as bile reflux [34,38,39]. However, elimination of duodenal gastroesophageal reflux has not been observed in all patients suggesting a role for persistent bile acids as a potential factor involved in refractory reflux symptoms despite PPI therapy. Indeed, a study including patients with persistent heartburn and regurgitation on a single PPI dose showed that a significant number of symptoms occurred in association with bile rather than acid reflux [40]. Using combined pH and Bilitec monitoring, the addition of Bilitec significantly increased the diagnostic yield of ongoing pathological reflux compared to pH alone from 27% to 67% respectively, in symptomatically GERD patients on PPIs [30].

The fact that the availability of the technique is very limited in common clinical practice and that dietary restriction during the test are required, the future of this test remains to be elucidated in further studies.

Esophageal impedance-pH monitoring

Esophageal impedance monitoring identifies retrograde bolus transit and can detect the nature and proximal extent of reflux. The technique is based on measurement of electrical impedance between multiple electrodes positioned along the axial length of a thin intraluminal probe. Impedance monitoring is not able to detect acidity or volume of reflux contents. Therefore, a pH electrode is typically incorporated into impedance catheter. Combined impedance-pH allows the detection of all types of reflux and the characterization into categories of acid and non-acid reflux; the latter can be subdivided in weakly acid and weakly alkaline reflux. Acid reflux has been defined as a reflux event associated with drop in esophageal pH <4, weakly acid when associated with a pH drop between 4 and 7 and weakly alkaline when reflux event is not associated with a pH drop <7 [41].

It is suggested that diagnostic yield of pH monitoring on PPIs for acid reflux is low since most reflux episodes under these circumstances are weakly acidic and therefore acid reflux is not detected [26]. Thus, impedance-pH monitoring is more sensitive than pH alone in the evaluation of patients with persistent reflux symptoms on PPIs. A large multicenter study in 168 refractory GERD patients showed that 16 (11%) of the 144 patients who had symptoms during the study had a positive SI for acid reflux and 53 (37%) had a positive SI for non-acid reflux. Thus, the diagnostic yield of combined testing compared to pH alone increased to 48% from 11%, respectively [42]. A recent study confirmed the value of combined impedance-pH showing that 39% of patients on double daily PPI therapy had a positive SI for non-acid reflux and would have been misdiagnosed by a pH-alone study [43]. These data support the idea that combined impedance-pH monitoring could identify more patients in whom reflux is the cause of their symptoms under PPIs compared to pH alone.

Similar results were observed in a European study evaluating patients on and off PPI therapy [44]. In patients off PPIs, impedance-pH added only a 4% increase to the diagnostic yield when compared with pH alone. However, in patients on PPIs, adding impedance to pH monitoring improved the diagnostic yield by 17%. In contrast, a recent study comparing the yield of impedance-pH monitoring off and on PPIs in patients with refractory GERD showed that the off PPI approach offered the best chance to assess the relationship between symptoms and reflux events [45]. The main limitation of this study was the cessation of PPI treatment for only 7 days prior to impedance-pH testing. In contrast to the above mentioned study, another study compared the results of impedance-pH in patients with refractory GERD on double PPI therapy with those of wireless pH testing in the same patients off PPI therapy [46].

The study showed that abnormal impedance in patients on therapy predicts acid reflux in patients off and suggested that combined impedance-pH monitoring provides the single best strategy for evaluation of reflux symptoms.

Very few studies assessed the value of esophageal impedance-pH monitoring in patients who failed PPI once daily. A recent study in a Greek population, the majority of which were on single PPI dose, showed that the use of combined impedance-pH monitoring substantially increased the diagnostic yield compared to pH alone. With SI analysis, 20.5% of patients received a diagnosis that could not have been achieved with pH testing [47].

Because impedance-pH monitoring is considered the most sensitive test for reflux detection, a negative study rules out GERD as a cause of persistent symptoms. However, patients whose symptoms are associated with acid or weakly acid reflux and who do not have abnormal esophageal acid exposure meet the criteria of hypersensitive esophagus and can be diagnosed with combined impedance-pH testing. Indeed, a recent study including 252 patients with reflux symptoms despite taking PPIs twice daily showed that 75 patients had hypersensitive esophagus [48]. From these patients, 58 (77.33%) had non-acid reflux only suggesting a temporal relationship between non-acid reflux and symptoms. However, the accuracy of symptoms indices for non-acid reflux events on PPIs has not been clearly established. It is also still debatable whether other impedance parameters such as esophageal bolus exposure and/or high number of reflux episodes should be used. In a recent study only 35% of patients with refractory symptoms had a normal recording when an abnormal high number of reflux episodes were taken into account compared to 53% when symptom association was used as a marker of GERD presence [49]. This study also suggests that patients with refractory heartburn and normal pH and negative symptom association indices during pH-impedance monitoring performed on therapy should be considered as having functional heartburn. Further studies are needed in order to determine the best parameter to be used in clinical practice for classification of patients with persistent heartburn. To date, there is only one study, in an abstract form, with normal impedance-pH values on double PPI dose [50].

Three recent studies have suggested that a positive SI during pH-impedance monitoring in patients with refractory reflux symptoms performed on PPI could predict a favorable response to medical or surgical treatment. Mainie *et al* followed 19 patients who were refractory to double-dose of PPI and successfully underwent laparoscopic Nissen fundoplication. Prior to surgery, 18 of 19 patients had a positive SI on esophageal pH-impedance monitoring. After a mean follow-up of 14 months, 16 of the patients with positive SI were asymptomatic [51]. Becker *et al* assessed 56 patients with persistent symptoms on a single dose of PPI and abnormal pH-impedance monitoring. Most of these patients had a positive SI and demonstrated a significantly higher response rate to doubling the PPI dose compared to patients with normal pH-impedance monitoring [52]. An Italian study prospectively assessed the outcomes of laparoscopic 62 Nissen fundoplications in patients who were non-responders to PPI and had a positive pH-impedance test. The overall satisfaction rate was 98.3% [53].

Conclusions

Management of a patient with refractory GERD symptoms requires a high level of certainty about the initial diagnosis of GERD, so the utility of diagnostic tests based on identification of residual reflux, anatomical and histological abnormalities of the esophagus is of importance. Although various evaluative tests are available for patients who failed PPI therapy, none of them is considered as the gold standard. Upper endoscopy has a limited value in discovering GERD-related findings in patients with persistent GERD symptoms on PPIs. Esophageal pH monitoring is commonly performed in patients with refractory GERD symptoms, however only a minority of these patients continued to report symptoms due to ongoing acid reflux. Bilitec has a limited availability in clinical practice. There is evidence supporting the use of combined impedance-pH monitoring as a promising strategy for evaluation of symptomatic GERD patients on PPIs. It seems reasonable to propose that before embarking on impedance-pH monitoring on PPI therapy, the presence of GERD should have been previously demonstrated by pH testing off therapy.

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