Abstract

Clinical manifestations of gastroesophageal reflux disease (GERD) include heartburn, regurgitation, dysphagia, chest pain, cough and other extraesophageal symptoms. GERD is known to cause erosive esophagitis, Barrett esophagus and has been linked to the development of adenocarcinoma of the esophagus.

Currently upper gastrointestinal endoscopy is the main clinical tool for visualizing esophageal lesions. Since the majority of GERD patients do not have endoscopic visible lesions other methods are required to document the abnormal acid exposure in the distal esophagus. For many clinicians ambulatory esophageal pH monitoring is the gold standard in diagnosing GERD since it quantifies distal esophageal acid exposure and allows the evaluation of the relationship between symptoms and acid reflux.

The availability of highly selective gastric acid suppressive therapy led to the introduction of short trials of proton pump inhibitors (PPI) to diagnose GERD. PPI trials are often used as a first line diagnostic tool in clinical practice and in particular in the primary care settings. This development has a major influence in the type of patients referred to gastrointestinal specialists, the current trend being that gastroenterologists are asked to evaluate an increasing number of patients with persistent GERD symptoms while on PPI therapy. In these patients the question is whether the persistent symptoms are or not associated with reflux (acid or non-acid). In the recent years combined multichannel intraluminal impedance and pH (MII-pH) monitoring has become a clinical tool that permits the clarification of the mechanisms underlying the persistent symptoms on acid suppressive therapy.

Key words

Gastroesophageal reflux disease - upper GI endoscopy - pH-metry - multichannel intraluminal impedance and pH monitoring - proton pump inhibitors

Introduction

Gastroesophageal reflux disease (GERD) is a common, chronic gastrointestinal disorder in Europe and the United States (1). Epidemiologic studies indicate that approximately 40% of the adult US population experiences occasionally heartburn, the most common GERD symptom (2), while 20% of the US population reports heartburn weekly (3). In Romania, the prevalence of gastroesophageal reflux disease is estimated to be around 15-25%.

The diagnosis of GERD has evolved over the years influenced by technologic and therapeutic progresses. The clinical armamentarium for diagnosing GERD includes radiographic examinations using contrast dyes, endoscopy, catheters and capsules measuring intraesophageal pH and empiric treatment trials. The indications for various procedures have adapted to the clinical challenges and the type of GERD patients referred to gastrointestinal specialists. The purpose of this review is to discuss the time-honored diagnostic tools as well as the latest developments in the field of gastroesophageal reflux disease.

Upper GI series (barium esophagogram)

In the beginning of the 20th century physicians recognized the ability of visualizing internal organs using X-Rays. In time the methods have become more sophisticated and are currently an indispensable part of the clinical diagnostic armamentarium. For the evaluation of the hollow organs of the digestive tract radiologists use radio-opaque agents to enhance the contrast of these organs from other structures. Barium esophagograms have been used for many years to evaluate alterations of the esophageal structures.
While Barium esophagograms can reveal mucosal lesion defects they have been replaced to a great extent by methods allowing direct visualization of the esophagus (i.e. endoscopy). Still, barium esophagogram remains an important tool in diagnosing primary esophageal disorders such as achalasia, evaluated extrinsic compressions on the esophagus and evaluating the motility of the upper esophageal sphincter. In the diagnosis of GERD Barium esophagograms are helpful in diagnosing hiatus hernias, peptic esophageal strictures, the opening of the lower esophageal sphincter and allows the appreciation of esophageal peristalsis. The limitations of this method are related to the use of radiating energy and to providing only a certain degree of diagnostic information. With regards to gastroesophageal reflux disease the one finding reported by radiologists that should always be interpreted cautiously, is the presence of gastroesophageal reflux during videofluoroscopy. The main reason for this caution is the limited sensitivity and specificity of these findings. Limited amounts of gastroesophageal reflux can occur even in normal healthy volunteers and the radiographic examination evaluates only a short period of time.

**Upper GI endoscopy**

In 1946 Allison introduced the term “reflux esophagitis” as the consequence of gastric acid injury to the esophagus (4) and for many years this was considered the evidence of gastroesophageal disease. Esophagogastroduodenoscopy (EGD) is superior to upper GI series in order to identify erosive esophagitis and allows the grading of the severity of esophagitis. Most commonly used scales to grade erosive esophagitis are the Savary-Miller and the Los Angeles (LA) classification and the more recently proposed MUSE classification. In addition to identifying erosive esophagitis, EGD with biopsies is the method of choice in diagnosing Barrett esophagus, esophageal erosions due to causes other than GERD (i.e. viral esophagitis, eosinophilic esophagitis, Crohn’s disease etc.). Esophagogastroscopy also allows treating complications of reflux disease such as peptic strictures, esophageal hemorrhage. In the last years several endoscopic antireflux procedures have been developed for the treatment of GERD (i.e. Stretta, Endocinch, Gatekeeper etc.). Despite these advantages the use of upper GI endoscopy in the diagnosis of GERD is losing ground and the main reason for this trend is the availability of highly active acid suppressive therapy. Proton pump inhibitors (PPIs) are highly effective in treating erosive esophagitis healing up to 90% of patients according to large, double-blind randomized studies (5). Due to the favorable side-effect profile PPIs are frequently prescribed by primary care physicians for patients complaining of heartburn, acid regurgitation or other symptoms attributed to GERD and refer patients to gastrointestinal specialists mainly when they do not respond to acid suppressive therapy. Therefore by the time gastroenterologists perform an upper endoscopy in GERD patients on PPI therapy the exam is likely to reveal normal appearing mucosa.

**Ambulatory esophageal pH-metry**

Systems measuring the intraesophageal acid concentration (i.e. esophageal pH-metry) were developed in the 1960’s allowing to quantify the duration of esophageal acid exposure and to evaluate the relationship between symptoms and acid reflux. Esophageal pH monitoring is considered by many investigators the gold-standard to diagnose GERD. Currently the most accepted criterion to identify a gastroesophageal reflux during pH monitoring is a sudden decrease in intraesophageal pH from above to below 4.0. In the mid 1970’s Johnson and DeMeester published a set of normal values for pH monitoring including cut-offs to separate normal from pathologic esophageal acid exposure which are still accepted by many centers (6). Measuring esophageal acid exposure in the distal esophagus allows diagnosing gastroesophageal reflux disease even in the absence of endoscopic visible lesions. Esophageal pH-metry has been used over the years to evaluate the effects of acid suppressive medications and to perform comparisons between various agents. More recently wireless systems have become clinically available, improving the patients’ acceptance of this test and allowing esophageal pH monitoring for extended (up to 96 hours) periods of time (Fig.1). Currently the most accepted definition of a gastroesophageal reflux episode during esophageal pH monitoring is a sudden drop in pH from above to below 4.0 (Fig.2).

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**Fig.1** Esophageal pH monitoring using either catheter-based systems or wireless pH capsules.

The limits of esophageal pH monitoring are reached when it comes to evaluating patients with persistent symptoms on acid suppressive therapy. These limitations are the result of the facts that (1) PPI reduce the amount of esophageal acid exposure and (2) pH criteria for identifying gastroesophageal reflux episodes with a pH above 4.0 (i.e. non-acid or weakly acidic reflux episodes) do not have a good sensitivity and specificity. Therefore conventional pH
monitoring identifies only patients in whom PPIs provide insufficient acid suppression (i.e. less than 10% of patients; see below). In patients with normal esophageal acid exposure on PPI therapy, conventional pH monitoring cannot distinguish between patients in whom symptoms are due to weakly acidic or non-acid reflux and patients in whom symptoms are not related to gastroesophageal reflux.

**PPI trial**

The availability of acid suppressive medication (i.e. histamine-2 receptor antagonists and proton pump inhibitors) have had a major impact not only in the treatment but also in the diagnosis of reflux disease. Proton pump inhibitors (PPI) have become the preferred treatment option for patients with gastroesophageal reflux disease due to their high efficacy in healing erosive esophagitis and providing good symptom control. The good symptom control offered by these pharmacologic agents has led investigators to propose using a short course of PPIs (i.e. PPI trial) to diagnose GERD. The sensitivity and specificity of PPI trials range between 75-92% and 55-90% respectively. Due to their increasing acceptance among patients and physicians PPI trials are frequently used in the primary care setting in patients presenting with symptoms thought to be due to gastroesophageal reflux and are considered acceptable first line diagnostic tests in patients with typical, uncomplicated GERD (7). This approach has changed the spectrum of patients referred to gastrointestinal specialists. Currently, the majority of patients seen by gastroenterologists are patients with persistent reflux symptoms on PPI therapy. Managing patients with persistent symptoms on proton pump inhibitor (PPI) therapy represents a further challenge requiring new tools for understanding the mechanisms of these persistent symptoms.

**Table 1** Sensitivity and specificity of PPI trials including the dosage (mg), duration of trial and the number of subjects included in the study

<table>
<thead>
<tr>
<th>PPI</th>
<th>Dosage</th>
<th>Days</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>40-0-20</td>
<td>7</td>
<td>37</td>
<td>78%</td>
<td>86%</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20-0-20</td>
<td>7</td>
<td>135</td>
<td>75%</td>
<td>55%</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>60-0-30</td>
<td>7</td>
<td>40</td>
<td>78%</td>
<td>80%</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30-0-0</td>
<td>28</td>
<td>68</td>
<td>92%</td>
<td>67%</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20-0-20</td>
<td>7</td>
<td>35</td>
<td>75%</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Combined multichannel intraluminal impedance and pH monitoring (MII-pH)**

Silny first introduced multichannel intraluminal impedance monitoring as a novel method to detect intraluminal bolus movement in 1991 (8). Combined with pH multichannel intraluminal impedance and pH (MII-pH) monitoring has become a clinically available tool which can detect gastroesophageal reflux independent of pH (Fig.3) (9). This method exploits differences in electrical conductivity of the esophageal wall and intraluminal content to identify bolus presence. Using multiple impedance measuring segments it allows distinguishing swallows from reflux episodes and has changed the paradigm of reflux monitoring in the sense that pH is no longer used to detect reflux episodes. Reflux episodes are detected by MII as a
drop in impedance advancing in time from distally to proximally and pH data are used to classify the reflux episode as acid (pH <4) or non-acid (pH >4). Since acid suppressive therapy is thought to change primarily the pH of the refluxate without decreasing the total number of reflux episodes combined MII-pH is the ideal technique to monitor gastroesophageal reflux on acid suppressive therapy (10).

Among patients who have failed to respond to an empiric trial of PPI ambulatory, patients can be separated in whom symptoms are associated with acid reflux and non-acid reflux from those in whom symptoms are not associated with reflux (Fig.5).

In a large multicenter study including 168 patients referred for persistent symptoms on twice daily PPI (11) we analyzed the mechanism of persistent symptoms using combined MII-pH monitoring. On the day of monitoring, 144 (86%) patients recorded symptoms allowing the evaluation of the relationship between symptoms and reflux using the symptom index (i.e. number of symptoms preceded by a reflux within 5 minutes divided by the total number of symptoms (12). A positive symptom index (i.e. SI>50%) for acid reflux was found in 16 (11%) patients, a positive SI for non-acid reflux was noted in 53 (37%) patients while in the remaining 75 (52%) patients the persistent symptoms were not associated with reflux (i.e. negative SI). Conventional pH would have been able to identify the positive association of symptoms and acid reflux (i.e. in 11% of patients) However, it would not have been able to distinguish, in the remaining 89% of patients, those with symptoms associated with non-acid reflux from those with symptoms not related to reflux. Outcome studies are currently underway evaluating the clinical significance of the information provided by combined MII-pH monitoring.

**Summary**

Clinical tools to diagnose gastroesophageal reflux have evolved parallel to our understanding of the disease and...
therapeutic options. While endoscopy remains the main modality of identifying mucosal or intraluminal lesions and pH-metry is the main modality to quantify esophageal acid exposure in untreated patients, these clinical tools are of limited value in evaluating patients with persistent symptoms on acid suppressive therapy. Combined impedance-pH monitoring helps clarifying the mechanisms of persistent symptoms in patients on PPI therapy and allows separating patients with symptoms due to persistent acid or non-acid reflux from those in whom persistent symptoms are not related to reflux. Rather than being a replacement for currently available techniques, combined impedance-pH monitoring should be regarded as an addition to the clinical armamentarium in the diagnosis of GERD, with excellent chances of becoming the gold standard for evaluating patients with persistent symptoms on acid suppressive therapy.

References