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TOPIC HIGHLIGHT

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Advances in diagnostic testing for gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) contributes substantially to morbidity and to costs in the United States health care system. The burden of this disease has resulted in attempts at improving diagnosis and characterizing patients. Numerous research and technical advances have enhanced our understanding of both the utility and limitations of a variety of diagnostic modalities. The purpose of this review is to highlight recent advances in GERD diagnostic testing and to discuss their implications for use in clinical practice. Topics addressed include esophageal pH monitoring, impedance testing, symptom association analyses, narrow-band imaging, and histopathology.

Key words: Gastroesophageal reflux disease; pH impedance; pH monitoring; Symptom association

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common, chronic disease that affects up to 20% of the adult population in the United States[1]. It is the most frequent digestive system diagnosis in ambulatory care and at inpatient discharge[2]. GERD contributes in excess of $10 billion in annual direct health care costs, with the majority of cost attributed to proton pump inhibitors (PPIs)[2,3]. The substantial disease burden of GERD and recognition of PPI unresponsive patients has fostered numerous efforts to improve diagnostic and therapeutic monitoring modalities.

Research investigations have enhanced our understanding of both the utility and limitations of a variety of diagnostic modalities. Newer techniques for esophageal functional testing such as wireless pH capsule monitoring, duodenogastroesophageal (also referred to as alkaline or bile reflux) reflux detection, and esophageal impedance testing have been introduced over the past decade and are utilized in clinical practice. The American College of Gastroenterology, American Society for Gastrointestinal Endoscopy and American Gastroenterological Association have recently published updated reviews and guidelines on reflux management and monitoring[4-6]. This review highlights recent advances in GERD diagnostic testing and their utility in clinical practice. A literature search was conducted for English-language articles dealing with functional evaluation of the esophagus from 2008 to 2009. Databases included Medline and PubMed, with search

terms that included esophageal pH monitoring, GERD, and esophageal impedance.

ESOPHAGEAL pH MONITORING

Wireless capsule pH monitoring: Is it better than catheter systems?

A significant advance in pH recording has been the incorporation of an antimony electrode into a wireless capsule that transmits pH data to an external receiver *via* radiofrequency telemetry (433 MHz)[7,8]. Major advantages of the wireless system include patient tolerability and capability of performing extended recording periods of 2-4 d. Discomfort associated with conventional catheter electrodes can lead patients to minimize or avoid reflux-provoking stimuli such as meals and physical activity, thus decreasing the detection of abnormal acid exposure[9,10]. As a result of improved patient tolerability, the wireless pH system might provide a more accurate picture of an individual's acid exposure profile under more realistic conditions.

Several investigations have compared wireless to catheter-based pH monitoring. A recent study has evaluated simultaneous placement of the Bravo capsule and SlimLine catheter system in 55 patients referred with GERD symptoms and 53 healthy volunteers[11]. The Slimline system was removed after 24 h while the Bravo system recorded 48 h of data. The SlimLine catheter system recorded almost double the acid exposure time than the Bravo system in both patients and volunteers. A similar finding has been noted in previous studies[12,13]. There was correlation between pH values and a concordance of diagnostic yield of 82.1%. However, the authors argue that, due to a wide variation in repeated measurements and random variation, as measured by limits of agreement, the two methods are not interchangeable[11].

It is not clear from the study methods whether the increased acid detection by the SlimLine catheter system was due to a thermal calibration artifact intrinsic to the catheter pH recording system first reported in 2005[13]. This error has since been corrected. The SlimLine system also records a greater number of reflux events than does Bravo, which is related to a higher sampling frequency. This numerical difference has previously been shown to have a minimal effect on the overall acid exposure time[13,14]. Other potential explanations for the different measurements include lost data due to interrupted signal transmission by the wireless system, and movement of the pH sensor in the catheter system relative to the esophagogastric junction. The latter factor might be important given the axial shortening of the esophagus during swallowing, which could move the catheter electrode closer to or even transiently into the proximal stomach. The Bravo system was better tolerated and preferred by patients, although the investigators did report a failure rate of approximate 15% due to failure or premature detachment.

Prolonged monitoring: Is 4 d better than 1 d?

Extended pH monitoring using wireless technology might theoretically improve the detection of reflux and increase the sensitivity of testing. Several studies have demonstrated that increasing the recording period from 24 to 48 h increases the sensitivity of pH monitoring by 10%-26%[4,8]. Several studies have also consistently demonstrated higher acid exposure values on day 2 compared with day 1 with the wireless capsule. Although the differences are generally small, this might affect the interpretation in a subset of studies[11]. Most capsules are placed immediately after endoscopy, therefore, the observation raises concerns regarding the potential impact of conscious sedation on reflux detection in the time period immediately after endoscopy, when patients might be resting and avoiding typical activity.

Another advantage of a prolonged monitoring period is the ability to perform testing both on and off PPI therapy in a single study[15,16]. Controversy exists regarding whether pH monitoring is best done off or on PPI therapy, because there are advantages and disadvantages to each approach. Off-therapy testing evaluates the presence of abnormal acid exposure and maximizes symptom-reflux association owing to the greater number of symptom and reflux episodes. Off-therapy testing is used to document the presence of acid reflux in patients with non-erosive reflux disease, who are being considered for anti-reflux endoscopic or surgical therapy. Off-therapy testing is also employed for patients with a low index of suspicion for having reflux disease, such as those showing no symptomatic response to empiric trials of PPI therapy or those with atypical symptoms. In contrast, pH testing on PPI therapy can provide documentation of the effectiveness of PPI therapy.

The feasibility of pH monitoring for an extended duration was recently determined for 96 h (48 h off PPI therapy followed by 48 h on therapy) in 60 patients[16]. A single pH capsule was placed and calibrated to two separate receivers with the second receiver activated after 48 h upon initiation of PPI therapy. Reflux symptoms were also recorded. Complete 96-h data were available for 40 patients (67%) at completion of the study, with 20 patients having incomplete data transmission or early capsule detachment. A total of 14 patients had abnormal acid exposure in the first 48 h, and day 2 testing (off therapy) increased the detection of abnormal acid exposure by 10%. On PPI therapy, 39 out of 40 patients (97.5%) had complete normalization of acid exposure at day 4. In addition, three symptom association indices [symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP)] all decreased by day 4 on PPI therapy. Overall, the prolonged testing increased the detection of acid exposure and reflux events for symptom association measurements and allowed for evaluation of both acid exposure and symptom response to PPI therapy. Limitations of this approach included early capsule detachment in 15% and the need for two separate receivers. Updated models of the wireless pH capsule are expected to allow for prolonged 4-d recording with a single receiver.

pH sensor location: Is 5 cm the best site?

By convention, correct positioning of the catheter pH

electrodes is 5 cm above the proximal border of the lower esophageal sphincter (LES) and 6 cm above the squamocolumnar junction (SCJ) for the wireless pH capsule. These locations minimize potential noise from proximal stomach acid exposure, at the expense of decreased sensitivity. This is a particular concern for catheter- based systems in which esophageal shortening during deglutition results in relative movement of the pH sensor closer to the LES. Grigolon *et al*[17] recently have evaluated differences in subcardial pH measured at two different locations in GERD, as well as the role of hiatal hernia. Their study population consisted of 14 healthy volunteers and 11 and 10 GERD patients with and without a hiatal hernia, respectively. Wireless pH monitoring was performed using the Bravo capsule 2 cm below the SCJ, and all patients received a standardized lunch after placement of the capsule. The investigators confirmed that subcardial pH was highly acidic in the early stage after meals, but there was no difference between healthy subjects and GERD patients. The presence of a hiatal hernia did not affect the results. The findings build upon important observations made by this group regarding the role of the "acid pocket" in the pathogenesis of GERD. In clinical practice, substantial intrapatient variability and interpatient heterogeneity have limited the utility of intragastric pH monitoring.

Another study has evaluated 48-h pH recording, off PPI therapy, immediately above the SCJ compared to simultaneous results obtained at 6 cm above the SCJ in 62 patients with reflux symptoms and 55 controls[18]. GERD patients included those with erosive disease as well as non-erosive patients with typical reflux symptoms that are responsive to PPI therapy. Using a pre-defined specificity of 90%, monitoring immediately above the SCJ increased the sensitivity from 63% to 86% in all patients. The total percentage of time that pH was < 4 for the entire 48-h study was the parameter that best discriminated between GERD patients and controls. Patients with and without esophagitis had an increased sensitivity (78% to 97% and 47% to 73%, respectively) that indicated an increased discriminatory power for patients with more severe disease. These results were similar to another study in which pH measurements were obtained simultaneously 6 and 1 cm above the gastroesophageal junction (GEJ) in 40 GERD patients with and without erosive disease[19]. The investigators found improved diagnostic accuracy in patients with erosive disease but not non-erosive reflux disease (NERD). Although the results of these studies are encouraging for increasing the sensitivity of pH testing, especially in patients with more severe disease, more validation is needed before changing the conventional location of pH measurements.

pH-IMPEDANCE TESTING

Theoretical advantages

Intraluminal impedance monitoring detects changes in the resistance to electrical current across adjacent electrodes positioned in a serial manner along a catheter. Multiple electrodes positioned along the axial length of the impedance catheter determine the proximal extent of a reflux event. It is capable of differentiating antegrade from retrograde bolus transit, as well as liquid from gas reflux. A pH electrode incorporated into the recording assembly allows for simultaneous detection of acid content. Patient tolerability is similar to conventional pH monitoring as this is a catheter- based system. Likewise, recording has been limited to 24 h.

There is considerable debate on the current role of pH-impedance testing in clinical practice[20-22]. As PPI use for GERD has increased, patients presenting with typical or atypical reflux symptoms in spite of PPI therapy, and without erosive esophagitis, often pose a diagnostic and management challenge. The association of non-acid reflux events with symptoms has been demonstrated in several studies[23-26]. Impedance-pH monitoring is the most sensitive technique for the detection of reflux events. As a result of the ability to detect, localize and classify reflux events as acidic, weakly-acidic or alkaline, simultaneously, pH-impedance testing has been posited as the future standard for reflux detection and monitoring[27]. In addition, the more comprehensive reflux detection could guide more individualized therapy in patients based on their reflux profile as well as predict response to medical or surgical treatment[20,21].

Although theoretically superior to pH monitoring, the clinical utility of combined pH-impedance monitoring is still being investigated. Conventional pH testing has demonstrated high sensitivity and specificity in patients with GERD and erosive esophagitis. The chemical nature of non-acid reflux does not allow the presence of mucosal erosions to be used in the determination of sensitivity and specificity of impedance data. Therefore, studies that have examined the utility of impedance testing have relied upon symptom-reflux association methodology to support the clinical significance of non-acid reflux. As discussed below, substantial limitations for symptom-reflux association accuracy in the evaluation of acid reflux also apply to non-acid reflux. Furthermore, the reliance on symptom indices necessitates careful delineation of the specific symptom being evaluated. For instance, symptom association for regurgitation on PPI therapy is better detected by impedance testing than pH testing alone. However, the importance of non-acid reflux in generating symptoms of heartburn or chest pain is unclear. It has been demonstrated that the majority of persistent heartburn or chest pain events on PPI therapy are not related to either acid or non-acid reflux[26,28]. Extra-esophageal symptoms of globus, asthma and hoarseness might occur independent of individual reflux events and thus are inappropriate for reflux-symptom association analysis. GERD is often considered as a cause of chronic cough. Although studies have shown symptom correlation between cough and GERD, 50% of the cough episodes precede the individual reflux events, which demonstrates that cough-induced reflux occurs as often as reflux-induced cough[28].

Further difficulties in substantiating a role for pH-impedance monitoring arise from the absence of highly

effective, pharmacological therapies for non-acid reflux. Limited studies have used baclofen and baclofen analogs that inhibit transient LES relaxation. Surgical fundoplication is a more definitive means of arresting both acid and non-acid reflux, and ongoing studies are examining the use of pH-impedance results in predicting postoperative outcomes in refractory reflux patients. Additional limitations of impedance monitoring include low baseline impedance values generated by the mucosa of Barrett's esophagus and esophagitis, which make detection of liquid reflux problematic in such circumstances. Inaccuracies in the current versions of automated analysis software require careful and time consuming manual data correction[29].

Recent data

As a result of the ability to characterize acidity and determine number, duration, and location of reflux events, the majority of research using pH-impedance has focused on the challenges associated with diagnosing and treating NERD. A recent small study has evaluated 16 NERD patients with both pH-impedance and combined multiple pH monitoring in an effort to assess changes in reflux acidity and sensitivity to reflux events[30]. Compared to multiple site pH testing (at three locations), pH-impedance monitoring showed a small increase in sensitivity in detecting proximal reflux events. The authors reported that 30% of all distal acid reflux events became weakly acidic in the proximal esophagus, and a third of these events resulted in symptoms. Although the sample size was small, the results lend support to the concept of hypersensitivity in the proximal esophagus in a subset of NERD patients[31,32].

In a much larger study, Savarino *et al*[33] have evaluated the diagnostic utility of pH-impedance monitoring in 150 patients with NERD off PPI therapy. Among patients with normal distal esophageal acid exposure time, they found similar positive symptom associations for patients with acid reflux (15%) and non-acid reflux (12%). Twenty-six per cent of this group had a negative symptom association and were considered functional heartburn patients. The classification of patients with hypersensitive esophagus accorded by pH-impedance results (normal acid exposure time, positive symptom association) reduced the number of patients that would have been classified as having functional disease by 40%[33]. However, overall 87% of the 150 NERD patients had acid reflux identified as the etiology of their symptoms.

Impedance pH monitoring has also been used to compare reflux patterns between patients with erosive esophagitis and NERD[34,35]. In a small study of 26 patients, evenly split between NERD and erosive disease, pH-impedance monitoring did not reveal significant differences in mean reflux duration or the incidence of acid or non-acid reflux episodes. When stratified by type of reflux episode, patients with erosive disease did have slightly more liquid (mean 9 ± 2 *vs* 5 ± 1, $P = 0.07$) and acid (mean 9 ± 2 *vs* 4 ± 1, $P = 0.048$) reflux episodes in the supine position. Overall, pH-impedance could not discriminate between NERD and erosive esophagitis but this likely reflects the limited power of the sample size. In another study, Savarino *et al*[35] have compared a cohort of GERD patients with erosive and non-erosive disease with a control population and demonstrated increased acid exposure times, and frequencies of acid reflux events as well as proximal esophageal reflux extension, in both GERD subsets. Patients with erosive disease had a higher frequency and increased proximal migration of acid reflux events. Notably, the frequency of non-acid reflux events and their association with symptoms were similar in both erosive and non-erosive disease. Overall, the results of these studies lend further support to the argument for monitoring both acid and non-acid reflux episodes in further characterizing GERD and potentially directing management. However, the increased diagnostic yield of pH impedance over pH monitoring alone was limited and neither study has demonstrated that the increased detection results in improved patient therapeutic outcomes.

There has also been debate about whether pH-impedance monitoring should be performed on or off PPI therapy. This has recently been addressed in a small prospective study of patients with continued GERD symptoms on twice daily PPI therapy[36]. Using a randomized, crossover study design, combined 24-h pH-impedance monitoring was performed on (twice daily) and off PPI therapy for 7 d. Neither the number nor extent of reflux episodes was affected by PPI use. There were significantly more acidic reflux episodes off PPI therapy and more weakly acidic episodes on PPI therapy. However, there was lack of concordance between the SAP for both measurements, which was likely due to the small sample size of the study.

Ultimately, the benefit of using pH-impedance monitoring in routine clinical practice depends upon its ability to guide effective medical and surgical management. A prospective series of 12 patients in Switzerland evaluated using pH-impedance monitoring before and after anti-reflux surgery (mesh-augmented hiatoplasty)[37]. Although the sample size was small, the authors found that multichannel intraluminal pH-impedance monitoring significantly increased the number of reflux episodes detected before and after surgery compared to pH testing alone. There were also more patients identified as having a positive SI in the pH-impedance group. The study has found that pH-impedance monitoring provides increased data compared to pH testing alone, however, whether this information favorably affects management and long-term patient outcomes is yet to be determined. Future therapeutic trials using inhibitors of transient LES relaxation should provide valuable insights into the clinical significance of non-acid reflux.

SYMPTOM ASSOCIATION

Available methods

Three methods have been devised to use statistical calculations to correlate symptoms with acid reflux. Symptom correlation can be separately calculated for each symptom attributable to reflux, including heartburn, regurgitation

or chest pain. The application of symptom correlation to atypical reflux symptoms such as throat pain, hoarseness, cough and asthma is problematic given the lack of temporal association between such symptoms and individual reflux events. The first method developed was the SI[38], which involves dividing the number of symptoms associated with acid reflux events by the total number of symptoms, which yields a percentage. A second approach is the SSI[39], which divides the total number of reflux episodes associated with symptoms by the total number of reflux episodes. The third approach for symptom-reflux correlation is the SAP[40]. This involves constructing a contingency table with four fields: (1) positive symptom, positive reflux; (2) negative symptom, positive reflux; (3) positive symptom, negative reflux; and (4) negative symptom and negative reflux. Fisher's exact test is then applied to calculate the probability that the observed association between reflux and symptoms occurred by chance. An SAP value > 95% indicates that the probability that the observed association between reflux and the symptom occurred by chance is < 5%.

Both the SI and SSI do not take into account the total number of reflux and symptom events. Thus, in patients with very infrequent or frequent reflux episodes or symptoms, random, temporal associations between reflux and symptoms might produce an inaccurate result. Another important distinction between the methods is that the SAP determines the statistical validity of symptom-reflux associations, whereas the SI and SSI provide information on the strength of the association.

Does it work?

Past attempts to validate the utility of the symptom indices have shown conflicting results with some groups reporting correlation with PPI response[41,42], whereas others have shown high discordance rates of the indices and mediocre specificity and sensitivity[43]. As with any test used in clinical practice, reproducibility is paramount and this issue has been addressed recently in 21 patients with GERD symptoms[44]. The SI, SSI and SAP were determined in concert with 24-h pH-impedance monitoring. The SAP and SSI showed the highest reproducibility compared with the SI. The study was performed under "real world" conditions of ambulatory monitoring, which suggested that the symptom association indices, although far from ideal, can play a role in relating symptoms to reflux episodes. The limitations of symptom association and remaining cognizant of what the three methods do not measure should be considered before applying these in clinical practice. The symptom correlation tests should be viewed as complementary information that links symptoms with reflux events, which does not ensure response to either medical or surgical therapy.

OTHER MODALITIES AND ISSUES

Narrow-band imaging

Use of narrow-band imaging (NBI) to enhance the contrast between esophageal and gastric mucosa and improve visualization of the SCJ has been studied in GERD patients. NBI has been shown to increase reproducibility in grading esophagitis[45] and the ability to detect changes in the microvasculature at the SCJ[46]. More recently, a prospective study has evaluated the use of NBI to differentiate erosive esophagitis (EE) from NERD and controls[47]. A total of 107 patients underwent endoscopy with NBI. Compared to conventional endoscopy, NBI allowed for an increased detection of micro-erosions, vascularity, and mucosal islands ("pit patterns"). In terms of differentiating patients using these criteria, EE and NERD patients had a higher prevalence of micro-erosions and vascularity compared to controls. EE and NERD patients were only differentiated by an increased vascular surface in the absence of pit patterns (sensitivity 86.1%, specificity 83.3%). Although NBI with endoscopy is unlikely to serve as a standard for the diagnosis of GERD, it could serve as an adjunct in the classification of erosive and non-erosive disease.

Histopathology

The use of histological characteristics to help diagnose GERD, and specifically NERD, has garnered increased attention and has recently been reviewed[48]. Although there are limitations to many of the studies that have evaluated histology, dilation of the intracellular space (DIS) has emerged as a promising diagnostic marker of NERD[48,49]. There is also evidence that DIS can be affected by PPI treatment, potentially serving as a clinical endpoint in therapy. However, definitive histological parameters of DIS have yet to be defined for reflux disease. Histological parameters such as basal cell hyperplasia and papillae elongation have proven less sensitive or specific for GERD, but might ultimately play a role when used in combination with DIS[48,50]. Ultimately, histopathological characteristics will likely be used in concert with other modalities to diagnose and characterize GERD better.

Eosinophilic esophagitis as a confounder

Eosinophilic esophagitis (EoE) has been increasingly diagnosed in pediatric and adult populations over the past 15 years[51]. Patients can present with a variety of symptoms including dysphagia, food impaction, heartburn, and chest pain[52,53]. However, these symptoms are not specific for the diagnosis and it can be difficult to differentiate EoE from GERD. Presently, the diagnosis of EoE is defined by the combination of clinical symptoms and histological characteristics of mucosal eosinophilia (> 15 eosinophils/high-power field)[52]. Supportive features include the presence of mucosal rings, longitudinal furrows and exudates in the esophagus. Disorders such as hypereosinophilic syndrome, connective tissue disorders, GERD, drug hypersensitivity reactions or infectious esophagitis should either be excluded or deemed non-causal in the eosinophilia.

A recent retrospective case control study has evaluated clinical, endoscopic and histological characteristics that could differentiate GERD from EoE[54]. The combination of nine characteristics (age, dysphagia, food allergy,

esophageal rings, linear furrows, white plaques, no hiatal hernia, maximum eosinophil count, and eosinophil degranulation) differentiated GERD from EoE in their population[54]. However, as GERD is prevalent in approximate 20% of the United States population, it is inevitable that many patients will have coexisting disease[52,55]. Moreover, acid reflux itself might produce tissue eosinophilia or allow for allergen sensitization[56]. A significant proportion of suspected EoE patients respond both symptomatically and histologically to PPIs, which blurs the distinction between EoE and GERD even further[57,58].

CONCLUSION

As a result of complexities in phenotypic heterogeneity and pathophysiology, there is no single gold standard diagnostic modality for GERD. pH monitoring has the greatest accuracy in patients with typical heartburn and erosive esophagitis, but unfortunately, it suffers from significant limitations when applied to atypical manifestations in NERD patients. Advances in pH monitoring, most notably wireless pH capsule technology, have improved patient tolerability and allowed for prolonged recordings that allow for both detection of acid reflux and response to therapy. The sensitivity of pH monitoring might be enhanced by pH capsule positioning closer to the SCJ, but further validation is needed because of concerns for diminished diagnostic specificity. pH-impedance has clearly increased the understanding of acid and non-acid reflux pathophysiology. When combined with symptom indices, pH-impedance detection of weakly and non-acidic reflux has the potential to provide information that might guide management. Therapeutic trials that have demonstrated the predictive value of impedance data support this practice. Recent results using NBI and histopathology are of significance. Taken together, these methods lend themselves to a reductionist view of GERD, whereas patients are classified into better-defined sub-groups. This strategy could ultimately result in more effective, individualized management of GERD and improved outcomes.

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