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Parameters on Esophageal pH-Impedance Monitoring That Predict Outcomes of Patients With Gastroesophageal Reflux Disease

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BACKGROUND & AIMS: **pH-impedance monitoring detects acid and nonacid reflux events, but little is known about which parameters predict outcomes of different management strategies. We evaluated a cohort of medically and surgically managed patients after pH-impedance monitoring to identify factors that predict symptom improvement after therapy.**

METHODS: **In a prospective study, we followed up 187 subjects undergoing pH-impedance testing from January 2005 through August 2010 at Washington University in St. Louis, Missouri (mean age, 53.8 ± 0.9 y; 70.6% female). Symptom questionnaires assessed dominant symptom intensity (DSI) and global symptom severity (GSS) at baseline and at follow-up evaluation. Data collected from pH impedance studies included acid exposure time (AET), reflux exposure time (RET) (duration of impedance decrease 5 cm above lower esophageal sphincter, reported as the percentage of time similar to AET), symptom reflux correlation (symptom index and symptom association probability [SAP]), and the total number of reflux events. Univariate and multivariate analyses were performed to determine factors associated with changes in DSI and GSS after therapy.**

RESULTS: **Of the study subjects, 49.7% were tested on proton pump inhibitor (PPI) therapy and 68.4% were managed medically. After 39.9 ± 1.3 months of follow-up, DSI and GSS scores decreased significantly ($P < .05$). On univariate analysis, an abnormal AET predicted decreased DSI and GSS scores ($P \leq .049$ for each comparison); RET and SAP from impedance-detected reflux events ($P \leq .03$) also were predictive. On multivariate analysis, abnormal AET consistently predicted symptomatic outcome; other predictors included impedance-detected SAP, older age, and testing performed off PPI therapy. Abnormal RET, acid symptom index, or SAP, and numbers of reflux events did not independently predict a decrease in DSI or GSS scores.**

CONCLUSIONS: **Performing pH-impedance monitoring off PPI therapy best predicts response to antireflux therapy. Key parameters with predictive value include increased AET, and correlation between symptoms and reflux events detected by impedance.**

Keywords: PPI; GERD; Esophageal pH-Impedance Monitoring; Symptom-Reflux Correlation; Response to Therapy.

See editorial on page 892.

Combined esophageal pH-impedance monitoring detects bolus movement within the esophageal lumen, and detects reflux events independent of pH and with higher sensitivity.[1] Some investigators have reported that pH-impedance testing adds little value compared with pH testing alone unless performed on antisecretory therapy,[2,3] but other investigators have shown that testing off antisecretory therapy provides better clinical value.[4,5] Although there is no clear consensus regarding this, other investigators have suggested that the pretest likelihood of gastroesophageal reflux disease (GERD) and the indication for pH-impedance monitoring may help guide this determination.[6,7]

Investigators agree on the gain in detection of reflux events with pH-impedance testing over pH testing alone, but disagreement remains as to the precise role of

Abbreviations used in this paper: AET, acid exposure time; ARS, antireflux surgery; CI, confidence interval; DSI, dominant symptom intensity; GERD, gastroesophageal reflux disease; GPE, Ghillebert probability estimate; GSS, global symptom severity; IQR, interquartile range; PPI, proton pump inhibitor; RET, reflux exposure time; SAP, symptom association probability; SI, symptom index.

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pH-impedance testing in directing GERD management. This stems from the uncertainty regarding optimal management of nonacidic or weakly acidic reflux. Clearly, antisecretory therapy does not resolve nonacid reflux,[8] however, antireflux surgery (ARS) reduces all reflux events when successful.[9,10] In addition, symptom-reflux correlation with nonacid reflux events is reported to predict symptomatic improvement with ARS.[11,12] Nonetheless, it remains unclear whether acid-based or impedance-based reflux parameters maximize the predictive value of pH-impedance monitoring.

In this study, we evaluated acid-based and impedance-based parameters on pH-impedance testing in a mixed cohort of patients managed with both medical therapy and ARS, in whom symptom burden at initial testing and at follow-up evaluation was documented carefully in a prospective fashion. Our aim was to determine which pH-impedance parameters predicted symptomatic outcomes from medical and surgical antireflux therapy. A secondary aim was to determine if testing on or off antisecretory therapy offered unique advantages in either of these cohorts.

Methods

Subjects

All adults (age, $\geq$18 y) with persisting GERD symptoms despite antisecretory therapy referred for pH-impedance testing from January 2005 through August 2010 were eligible for inclusion. Exclusion criteria included inadequate studies (poor data quality precluding analysis), incomplete studies ($<$14 hours of recording time), presence of histopathology-based esophageal motor disorders (achalasia spectrum disorders, so-called *scleroderma esophagus*), prior history of fundoplication or other esophageal surgery, and lack of follow-up evaluation for post-therapy symptom assessment. Each patient's referring physician was responsible for patient management, taking into account the pH-impedance results; treatment decisions were not influenced or altered by the study investigators. This study protocol was approved by the Human Research Protection Office (institutional review board) at Washington University in St. Louis.

Symptom Burden

Symptom burden was assessed both for the dominant presenting symptom identified by the patient, and globally in terms of esophageal symptomatic status, determined by symptom survey before pH-impedance testing. Dominant and secondary symptom frequency and severity were rated on 5-point Likert scales generated a priori for esophageal testing at our center and used in previous publications[4,13–15] and validated for assessment of esophageal symptoms.[14] Patients rated symptom frequency from 0 (no symptoms) to 4 (multiple daily episodes) and symptom severity from 0 (no symptoms) to 4 (very severe symptoms). Symptom intensity then was calculated as the product of the frequency and severity of a particular symptom, for a score from 0 to 16. For the purpose of this study, symptom intensity extracted for the dominant symptom was termed *dominant symptom intensity* (DSI). Overall esophageal symptomatic status (global symptom severity [GSS]) was assessed using a 100-point visual analog scale.

Symptom burden was assessed initially at the time of the pH-impedance study. Potential subjects for this study were contacted prospectively to evaluate management approaches (surgical vs medical therapy) and symptomatic outcomes by an investigator (A.P.) who was not involved in the management of the patients. The pre-procedure symptom survey was re-administered, and changes in DSI and GSS were calculated to assess symptomatic outcomes.

pH-Impedance Monitoring

pH-impedance testing at our center is open access, wherein referring physicians decide whether testing is performed on or off antisecretory therapy; both groups were included in this study. Patients tested off therapy were instructed to stop their proton pump inhibitor (PPI) medications 7 days before the study, and histamine-2–receptor antagonists, prokinetic medications, and antacids 3 days before the study. After an overnight fast, an experienced nurse positioned the pH-impedance catheter (Sandhill Scientific, Highlands Ranch, CO) so that the distal esophageal pH sensor was 5 cm proximal to the lower esophageal sphincter, identified using high-resolution esophageal manometry. During data acquisition, patients recorded their meals and activities, and logged their symptom events electronically. Data then were analyzed with dedicated software (Bioview Analysis; Sandhill Scientific), which calculated the numbers of reflux events, exposure times, and symptom-reflux association parameters. Each pH-impedance study was scrutinized further manually by 2 reviewers (A.P., C.P.G.) to ensure the automated capture of reflux events was accurate; discrepancies between the reviewers were resolved by discussion.

Acid exposure time (AET) was calculated as the percentage of time the pH was less than 4 at the distal esophageal pH sensor; an AET of 4.0% or greater was designated as abnormal per our institutional threshold.[4] Reflux exposure time (RET) consisted of the percentage of time refluxate was in contact with the distal esophageal impedance electrodes located at 5 cm above the LES; the validated threshold of RET of 1.4% or greater was considered abnormal.[16]

Symptoms were considered related to reflux events if they occurred within 2 minutes after the reflux event. The symptom index (SI) was calculated as a ratio of reflux-related symptoms to the total number of symptoms, and designated as positive if 50% or greater.[17]