Published in final edited form as:

Clin Gastroenterol Hepatol. 2015 May ; 13(5): 884–891. doi:10.1016/j.cgh.2014.08.029.

Parameters on Esophageal pH Impedance Monitoring that Predict Outcomes of Patients with Gastroesophageal Reflux Disease

Amit Patel, MD, Gregory S. Sayuk, MD, MPH, and C. Prakash Gyawali, MD, MRCP

Division of Gastroenterology, Washington University School of Medicine, Saint Louis, Missouri

Abstract

Background & Aims: pH impedance monitoring detects acid and non-acid 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 following pH-impedance monitoring to identify factors that predict symptom improvement after therapy.

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

Results: Of study subjects, 49.7% were tested on proton pump inhibitor (PPI) therapy and 68.4% were managed medically. After 39.9±1.3 months follow up, DSI and GSS scores decreased significantly ($P<.05$). On univariate analysis, abnormal AET predicted decreased DSI and GSS scores ($P=.049$ for each comparison); RET and SAP from impedance-detected reflux events ($P=.03$) were also 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 decrease in DSI or GSS scores.

© 2014 The AGA Institute All rights reserved

Address all correspondence to: C. Prakash Gyawali, MD, Professor of Medicine, Division of Gastroenterology, 660 South Euclid Ave., Campus Box 8124, Saint Louis, MO 63110, Phone: 314-454-8201, Fax: 314-454-5107 cprakash@dom.wustl.edu. Author roles: AP: study design, data collection and analysis, manuscript preparation and review; GSS: study design, data analysis, critical review of manuscript; CPG: study concept and design, data analysis, manuscript preparation, critical review and final approval of manuscript. No conflicts of interest exist with any of the authors.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Podium Presentation in Preliminary Form at the Distinguished Abstract Plenary, Annual Meeting of the American Gastroenterological Association Chicago, May 2014

Conclusion: Performing pH impedance monitoring off PPI therapy best predicts response to anti-reflux 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

INTRODUCTION

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 over pH testing alone unless performed on antisecretory therapy ^{2, 3}, but others demonstrate testing off antisecretory therapy provides better clinical value ^{4, 5}. While there is no clear consensus regarding this, yet others suggest that the pretest likelihood of 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 pH-impedance testing in directing GERD management. This stems from the uncertainty regarding optimal management of non-acidic or weakly acidic reflux. Clearly, antisecretory therapy does not resolve non-acid reflux ⁸, while antireflux surgery (ARS) does reduce all reflux events when successful ^{9, 10}. Additionally, symptom-reflux correlation with non-acid 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, where symptom burden at initial testing and upon follow-up was carefully documented in a prospective fashion. Our aim was to determine which pH-impedance parameters predict symptomatic outcomes from medical and surgical antireflux therapy. A secondary aim was to determine if testing on or off antisecretory therapy offers unique advantages in either of these cohorts.

METHODS

Subjects

All adults (≥ 18 years of age) 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 (less than 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 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 prior to 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 symptoms¹⁴. Patients rate 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 is then 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 initially assessed at the time of the pH-impedance study. Potential subjects for this study were prospectively contacted to evaluate management approaches (surgical versus medical therapy) and symptomatic outcomes by an investigator (AP) not involved in management of the patients. The pre-procedure symptom survey was readministered, 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 are instructed to stop their PPI medications 7 days prior to the study, and histamine-2 receptor antagonists, prokinetic medications, and antacids 3 days prior to the study. After an overnight fast, an experienced nurse positions the pH-impedance catheter (Sandhill Scientific, Highlands Ranch, CO) so that the distal esophageal pH sensor is 5 cm proximal to the lower esophageal sphincter, identified using high resolution esophageal manometry. During data acquisition, patients record their meals and activities, and log their symptom events electronically. Data is then analyzed with dedicated software (Bioview Analysis; Sandhill Scientific, Highlands Ranch, CO), which calculates the numbers of reflux events, exposure times, and symptom-reflux association parameters. Each pH-impedance study was further scrutinized manually by two reviewers (AP, CPG) 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 below 4 at the distal esophageal pH sensor; an AET 4.0% was designated as abnormal per our institutional threshold⁴. 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 1.4% was considered abnormal ¹⁶.

Symptoms were considered related to reflux events if they occurred within 2 minutes following the reflux event. Symptom index (SI) was calculated as a ratio of reflux-related symptoms to the total number of symptoms, and designated as positive if 50% ¹⁷. Symptom association probability (SAP) was calculated using the Ghillebert probability estimate (GPE) as previously described ¹⁸⁻²¹. Our group has previously demonstrated excellent concordance between the GPE and SAP calculated by the standard Wuesten method, with major discordance in only 2.8%, suggesting that these two metrics may be used interchangeably ²². Unlike the Wuesten method, GPE can be calculated from summary pH or pH impedance parameters. The SAP was designated positive if the likelihood of a chance association between the symptom and reflux events was <5%, corresponding to an SAP of >95% or $p < 0.05$. The SI and SAP were each calculated for pH-detected reflux events, then re-calculated for impedance-detected reflux events.

Data Analysis

Data are reported as the mean $\pm$ standard error of the mean (SEM) for normally distributed data, and as median (interquartile range, IQR) for skewed data. Categorical data were compared using the χ -squared test, Fisher's exact test, or the Mann-Whitney U test as appropriate. Grouped data were compared using the 2-tailed Student's *t*-test. Univariate and multivariate analyses were performed to identify findings that predicted an improved symptomatic outcome, measured as both linear DSI and GSS change and 50% (dichotomized) DSI or GSS improvement. Linear and logistic regression models were created as appropriate to determine predictors of a successful symptomatic outcome, and included clinical and demographic data as well as acid and impedance parameters. In all cases, $p < 0.05$ was required for statistical significance. All statistical analyses were performed using IBM SPSS Statistics V.22.0 (Armonk, NY).

RESULTS

Over the 5-year study period, 302 subjects underwent ambulatory pH-impedance testing for GERD symptoms. Inclusion criteria were not met by 60 patients (7 had inadequate or incomplete studies, 26 had undergone fundoplication or other esophageal surgery, 3 had evidence of major esophageal motor disorders, and 24 were missing pre-procedure symptom surveys), 53 could not be successfully reached for follow-up, and 2 declined to participate; these 115 patients were excluded from the study. The remaining 187 subjects (53.8 $\pm$ 0.9 years, 70.6% female, 85.0% Caucasian) consented to participate in the study and composed the study sample (Table 1).

Subjects and symptom burden

Of the 187 total subjects, 114 (61.0%) presented with typical symptoms (heartburn or regurgitation), while 73 (39.0%) presented with atypical symptoms (chest pain, cough, hoarseness, or wheezing). However, age, gender, race, duration of follow-up, proportions managed surgically, PPI status on testing, and baseline GSS did not differ by symptom

presentation ($p = 0.11$ for each comparison). Testing on or off antisecretory therapy was evenly divided (50.3% tested off therapy, 49.7% on therapy). Subjects tested on and off antisecretory therapy did not differ in terms of age, gender, race, typical symptom presentation, duration of follow-up, baseline global symptom burden, or proportions managed surgically ($p = 0.09$ for each comparison). Two-thirds of the subjects were managed medically with antisecretory therapy (68.4%), while the remaining 31.6% underwent ARS, at the discretion of the treating physicians. The surgical and medical groups did not differ in terms of age, gender, race, symptom presentation, baseline global symptom burden, duration of follow-up, or PPI status on pH-impedance testing ($p = 0.07$ for each comparison, Table 1).

Symptom burden as measured by DSI and GSS was high for the entire study cohort (Table 1). Subjects with atypical symptom presentation had worse baseline DSI (median 12, IQR 5.5-16) compared to those with typical symptoms (median 8, IQR 4-12, $p=0.018$), but GSS did not differ by symptom pattern (atypical: median 68, IQR 49-85 vs. typical: median 65, IQR 43-79, $p=0.4$). Symptom burden was similar regardless of antisecretory status at testing (median DSI 9, IQR 4-16 off therapy vs. 8, IQR 4-16 on therapy, $p=0.4$; median GSS 65, IQR 48-83 vs. 66.5, IQR 42.5-81 respectively, $p=0.8$).

Abnormal pH and impedance parameters

Of the total cohort, 64 (34.2%) had an abnormal total AET and 103 (55.1%) had an abnormal RET (Table 2). Symptom-reflux correlation was identified cumulatively in 58.8% (positive SI: 42.8%, positive SAP: 49.7%). Positive symptom-reflux correlation was higher for impedance-detected reflux events compared to pH-detected reflux events (SI: 42.8% vs 19.3%, respectively, $p<0.001$; SAP: 47.6% vs 28.9%, respectively, $p<0.001$). Overall, reflux evidence with symptom correlation was demonstrated in 39.6% (16.0% with pH data alone, 36.9% with impedance data alone). Subjects tested off antisecretory therapy had significantly higher rates of abnormal AET, positive acid SI, positive acid SAP, and positive impedance SAP, when compared to those tested on antisecretory therapy (Table 2). However, subjects tested on and off antisecretory therapy had similar rates of abnormal RET, positive impedance SI, and established thresholds for total numbers of reflux events ($p = 0.41$ for each comparison, Table 2).

As would be expected, surgically managed patients had greater proportions of abnormal pH and impedance parameters, including abnormal AET, abnormal RET, positive symptom-reflux correlation (SI and SAP) with both acid-detected and impedance-detected reflux events, and elevated total numbers of reflux events, compared to medically managed patients (Table 1).

Symptom Improvement with Therapy

After follow-up of 39.9 ± 1.3 months after testing, mean GSS improved by 55.2%, with 54.9% of subjects reporting 50% GSS improvement (Figure 1). DSI improved by 57.8%, with 68.2% of subjects reporting 50% improvement in dominant symptom intensity. Surgically managed patients had higher rates of linear and dichotomous GSS and DSI improvement (Figure 1, $p = 0.03$ for each comparison with medically managed patients). Subjects tested off PPI therapy had higher rates of linear and dichotomous GSS

improvement on follow up ($p = 0.02$ for each comparison with subjects tested on PPI), but rates of linear and dichotomous DSI improvement were similar ($p = 0.4$ for each comparison). Rates of symptom improvement did not differ between typical and atypical symptom presentations ($p = 0.15$ for each comparison).

Predictors of symptom improvement

On univariate analysis, AET (linear or dichotomized by AET of 4%) was a significant predictor of linear symptom improvement as assessed by both DSI and GSS (Tables 3 and 4). This generally held true for both medical and surgical management. RET and SAP from impedance detected reflux events also predicted linear DSI and GSS improvement. At a global level, other acid and impedance parameters did not predict linear DSI or GSS improvement (Tables 3 and 4). There were no predictors of 50% DSI improvement on univariate analysis. When 50% GSS improvement was assessed, AET (both linear and dichotomous), linear RET, and symptom-reflux association with impedance detected reflux events predicted symptom improvement. Reflux events >73 trended strongly towards predicting linear GSS change (Table 4); otherwise, numbers of reflux events using established thresholds on an off PPI therapy did not predict symptom improvement.

On multivariate analysis controlling for demographics, symptom presentation, PPI status and reflux parameters that predicted symptom change on univariate analysis (abnormal AET, abnormal RET, positive SAP calculated for both acid-detected and impedance-detected reflux events, and elevated number of reflux events), only abnormal AET (risk ratio 2.3, 95% CI 0.3-4.3, $p=0.027$) predicted linear DSI improvement, and only abnormal AET (risk ratio 17.1, 95% CI 6.3-27.9, $p=0.002$) and positive SAP calculated from impedance detected reflux events (risk ratio 13.4, 95% CI 1.6-25.1, $p=0.026$) predicted linear GSS improvement (Figure 2A). However, abnormal RET, positive acid SAP, and thresholds for total numbers of reflux events did not ($p = 0.47$ for each comparison). Further, abnormal AET (odds ratio 2.6, 95% CI 1.2-5.6, $p=0.014$), testing off PPI therapy (odds ratio 2.4, 95% CI 1.1-5.0, $p=0.026$), and older age (odds ratio 1.03, 95% CI 1.004-1.06, $p=0.027$) predicted 50% GSS improvement for the total cohort; there were no independent predictors of 50% DSI improvement (Figure 2B).

Multivariate analyses were separately performed using similar models for subjects tested off and on antisecretory therapy. For subjects tested off antisecretory therapy, abnormal AET (risk ratio 3.6, 95% CI 1.0-6.4, $p=0.01$) predicted linear DSI improvement; abnormal AET (risk ratio 17.8, 95% CI 1.5-34.1, $p=0.033$) and impedance SAP (risk ratio 20.1, 95% CI 1.0-39.3, $p=0.04$) predicted linear GSS improvement. No factors retained significance for predicting 50% DSI or GSS improvement off therapy. In patients tested on antisecretory therapy, no factors predicted linear DSI or GSS improvement; older age (odds ratio 1.1, 95% CI 1.01-1.12, $p=0.11$) predicted 50% DSI improvement, and abnormal AET (odds ratio 4.3, 95% CI 1.3-14.2, $p=0.017$) once again predicted 50% GSS improvement.

DISCUSSION

In this report, we show that abnormal AET has higher clinical value compared to impedance-based reflux parameters in predicting symptomatic response in reflux disease.

However, impedance-based symptom-reflux correlation parameters have utility in complementing acid parameters to maximize predictive value. Our univariate and multivariate analyses demonstrate that abnormal AET predicted linear and dichotomous GSS improvement, whereas abnormal dichotomous RET did not attain predictive significance in any analysis. Established thresholds for total numbers of reflux events did not predict linear or dichotomous GSS improvement. Our data therefore suggests that performing pH-impedance testing off PPI therapy increases the yield of abnormal AET and symptom-reflux association with reflux events, facilitating predictive value for symptom improvement with both medical and surgical antireflux therapy.

Traditional pH parameters have well-established predictive value in GERD, with increasing AET correlating with a higher degree of esophagitis ²³, and abnormal pH parameters predicting symptomatic response to antisecretory therapy ²⁴ and with ARS ²⁵. However, outcome data for impedance parameters is lacking in the literature, despite the increased diagnostic yield of pH-impedance testing over pH testing alone ^{26, 27}. In particular, low numbers of reflux events on impedance testing can be misleading, as a few long reflux events could significantly elevate acid exposure times. We demonstrate that acid parameters continue to have strong predictive value in determining symptom improvement following any therapy of reflux. Although thresholds have been derived for reflux exposure (i.e. RET) in the distal esophagus ¹⁶, this parameter did not hold up to AET on multivariate analysis despite longer RET being associated with better symptomatic outcomes on univariate analysis. Our data suggests that the best value from the impedance component of pH-impedance monitoring is in detecting reflux events, and thereby improving correlation of symptoms to reflux events. The implications of these findings are that if pH-impedance monitoring is being performed to predict symptomatic outcome from therapy, testing off antisecretory therapy offers the best parameters in making this determination, regardless of whether medical or surgical management is planned. Within this paradigm, acid based parameters, particularly the acid burden carries the most weight.

Although only limited outcome data suggest a relationship between non-acidic reflux and GERD symptoms, we found that SAP calculated for impedance-detected reflux events had predictive value for both dominant symptom improvement and global improvement. Some have advocated caution to not over-interpret the increased rates of symptom-reflux correlation afforded by impedance testing ²⁸, since these parameters constitute the weakest link in currently used reflux parameters. Further, symptom-reflux association cannot be determined for constant symptoms like hoarseness, globus, or sore-throat. Our current data supports previous reports that symptom-reflux correlation has value when positive^{21, 29}; we acknowledge that these parameters arguably do not add value when negative. Since impedance-detected reflux events are shorter in duration than acid-detected reflux events which require resolution of mucosal acidification, symptom correlation is more specific than with acid-detected reflux events. Further, if reflux symptom generation involves mechanical stretch and not just chemical stimulation from acidic reflux events, it is likely that pH testing alone will miss many reflux events. Hence, we concur with available data that impedance parameters, particularly symptom-reflux association, can complement established acid parameters in predicting symptomatic outcome in GERD.

We report a dichotomy between DSI and GSS in assessing symptom outcome. Despite improvement in DSI comparable to GSS following both medical and surgical therapy, reflux parameters did not predict DSI improvement as well as GSS improvement. This variability is potentially because reflux disease involves more than just one dominant symptom, and there is a global sense of esophageal well-being that patients expect with reflux management. This phenomenon may be especially true when both typical and atypical symptoms coexist, or when both perceptive (e.g. heartburn, chest pain) and transit (e.g. regurgitation) symptoms coexist. Further studies tracking a composite of symptoms are needed to further dissect this phenomenon as it relates to assessing therapeutic response.

A few limitations of our study design constrain the strength of our conclusions, especially those related to retrospective patient identification. For example, we could not accurately corroborate the frequency of or compliance with antisecretory therapy on an individual basis, both prior to pH-impedance testing, and in medically managed patients. We tried to overcome these limitations by utilizing patient-reported symptoms, and objective measures from pH-impedance studies. Despite this, we could not determine factors that drove management decisions towards medical or surgical management, as management was left to treating physicians, who utilized findings from pH-impedance testing as well as patient and physician preference to make their management decisions. Non-reflux processes such as functional pain syndromes and placebo effect could also have influenced positive outcomes, but these could not be further assessed within the confines of our study design. Despite these limitations, we believe that our findings reflect how pH-impedance testing is utilized in the “real world” setting and provide a foundation for planning future inquiries into the value and best uses of this technology.

In summary, we report that impedance based reflux parameters complement but do not replace acid based parameters in predicting symptom outcome from both medical and surgical antireflux therapy. Since abnormal AET and symptom-reflux correlation parameters are detected more often when testing is performed off therapy, pH-impedance testing off antisecretory therapy maximizes prediction of symptomatic outcome from GERD therapy.

Acknowledgments

This study was partially funded through NIH/NIDDK (5P30 DK052574-14 –AP; NIH K23DK84413-4 - GSS), and through the Washington University Department of Medicine Mentors in Medicine (MIM) and Clinical Science Training and Research (CSTAR) programs.

REFERENCES

Uncategorized References

1. Bredenoord AJ, Weusten BL, Timmer R, et al. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. *Am J Gastroenterol*. 2006; 101:453–9. [PubMed: 16464226]
2. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol*. 2006; 101:1956–63. [PubMed: 16848801]

3. Pritchett JM, Aslam M, Slaughter JC, et al. Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. *Clin Gastroenterol Hepatol*. 2009; 7:743–8. [PubMed: 19281866]
4. Patel A, Sayuk GS, Gyawali CP. Acid-based parameters on pH-impedance testing predict symptom improvement with medical management better than impedance parameters. *Am J Gastroenterol*. 2014
5. Hemmink GJ, Bredenoord AJ, Weusten BL, et al. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? *Am J Gastroenterol*. 2008; 103:2446–53. [PubMed: 18684197]
6. Pandolfino JE, Vela MF. Esophageal-reflux monitoring. *Gastrointest Endosc*. 2009; 69:917–30. 930 e1. [PubMed: 19249037]
7. Ates F, Vaezi MF. New Approaches to Management of PPI-Refractory Gastroesophageal Reflux Disease. *Curr Treat Options Gastroenterol*. 2014; 12:18–33. [PubMed: 24430334]
8. Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. *Gastroenterology*. 2001; 120:1599–606. [PubMed: 11375942]
9. Roman S, Poncet G, Serraj I, et al. Characterization of reflux events after fundoplication using combined impedance-pH recording. *Br J Surg*. 2007; 94:48–52. [PubMed: 17054312]
10. Frazzoni M, Conigliaro R, Melotti G. Reflux parameters as modified by laparoscopic fundoplication in 40 patients with heartburn/regurgitation persisting despite PPI therapy: a study using impedance-pH monitoring. *Dig Dis Sci*. 2011; 56:1099–106. [PubMed: 20737211]
11. Mainie I, Tutuian R, Agrawal A, et al. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg*. 2006; 93:1483–7. [PubMed: 17051602]
12. del Genio G, Tolone S, del Genio F, et al. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. *J Gastrointest Surg*. 2008; 12:1491–6. [PubMed: 18612705]
13. Stoikes N, Drapekin J, Kushnir V, et al. The value of multiple rapid swallows during preoperative esophageal manometry before laparoscopic antireflux surgery. *Surg Endosc*. 2012; 26:3401–7. [PubMed: 22648115]
14. Reidel WL, Clouse RE. Variations in clinical presentation of patients with esophageal contraction abnormalities. *Dig Dis Sci*. 1985; 30:1065–71. [PubMed: 4053917]
15. Kushnir VM, Prakash Gyawali C. High resolution manometry patterns distinguish acid sensitivity in non-cardiac chest pain. *Neurogastroenterol Motil*. 2011; 23:1066–72. [PubMed: 21929566]
16. Shay S, Tutuian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol*. 2004; 99:1037–43. [PubMed: 15180722]
17. Wiener GJ, Richter JE, Copper JB, et al. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol*. 1988; 83:358–61. [PubMed: 3348191]
18. Ghillebert G, Janssens J, Vantrappen G, et al. Ambulatory 24 hour intraoesophageal pH and pressure recordings v provocation tests in the diagnosis of chest pain of oesophageal origin. *Gut*. 1990; 31:738–44. [PubMed: 2370009]
19. Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology*. 1994; 107:1741–5. [PubMed: 7958686]
20. Prakash C, Clouse RE. Value of extended recording time with wireless pH monitoring in evaluating gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2005; 3:329–34. [PubMed: 15822037]
21. Kushnir VM, Sayuk GS, Gyawali CP. Abnormal GERD parameters on ambulatory pH monitoring predict therapeutic success in noncardiac chest pain. *Am J Gastroenterol*. 2010; 105:1032–8. [PubMed: 19920808]
22. Kushnir VM, Sathyamurthy A, Drapekin J, et al. Assessment of concordance of symptom reflux association tests in ambulatory pH monitoring. *Aliment Pharmacol Ther*. 2012

23. Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. *Gastroenterology*. 1996; 111:1192–9. [PubMed: 8898632]
24. Aanen MC, Weusten BL, Numans ME, et al. Effect of proton-pump inhibitor treatment on symptoms and quality of life in GERD patients depends on the symptom-reflux association. *J Clin Gastroenterol*. 2008; 42:441–7. [PubMed: 18344896]
25. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg*. 1999; 3:292–300. [PubMed: 10481122]
26. Zerbib F, Belhocine K, Simon M, et al. Clinical, but not oesophageal pH-impedance, profiles predict response to proton pump inhibitors in gastro-oesophageal reflux disease. *Gut*. 2012; 61:501–6. [PubMed: 21997546]
27. Moawad FJ, Betteridge JD, Boger JA, et al. Reflux episodes detected by impedance in patients on and off esomeprazole: a randomised double-blinded placebo-controlled crossover study. *Aliment Pharmacol Ther*. 2013; 37:1011–8. [PubMed: 23560727]
28. Slaughter JC, Goutte M, Rymer JA, et al. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2011; 9:868–74. [PubMed: 21782769]
29. Hersh MJ, Sayuk GS, Gyawali CP. Long-term therapeutic outcome of patients undergoing ambulatory pH monitoring for chronic unexplained cough. *J Clin Gastroenterol*. 2010; 44:254–60. [PubMed: 19826278]

Figure 1. Improvement in symptom burden, as measured by change in dominant symptom intensity (DSI) and global symptom severity (GSS) (* $p < 0.05$).

Figure 2.

Independent predictors of symptom improvement following management of reflux disease.

A. Prediction of linear change is depicted as risk ratios and 95% confidence intervals, values not crossing the zero axis are significant (* $p=0.027$ for DSI and $p=0.002$ for GSS; ** $p=0.026$ for GSS).

B. Prediction of $\geq 50\%$ improvement is depicted as odds ratios and 95% confidence intervals, values not crossing the value of 1 are significant (* $p=0.014$, ** $p=0.05$). In both instances, abnormal AET independently predicted symptom response following antireflux therapy; impedance-SAP complemented prediction, especially when GSS was used as the outcome measure.

Table 1

Baseline Demographics, Clinical Characteristics, and Proportions with Abnormal pH and Impedance Parameters by Treatment

Parameter	All subjects <i>n</i> =187	Surgical <i>n</i> =59	Medical <i>n</i> =128	<i>P</i> value
Mean age (yr)	53.8±0.9	54.9±1.2	53.3±1.3	0.433
Gender (F)	132, 70.6%	47, 79.7%	85, 66.4%	0.065
Race (Caucasian)	159, 85.0%	53, 89.8%	106, 82.8%	0.466
Typical symptoms*	114, 61.0%	41, 69.5%	73, 57.0%	0.105
Duration of follow-up (mo)	39.9±1.3	39.2±2.3	40.2±1.7	0.733
Tested on PPI	93, 49.7%	24, 40.7%	69, 53.9%	0.093
Symptom Intensity				
Baseline	9.0±0.4	10.2±0.7	8.4±0.5	0.044
Change**	-5.2±0.5	-7.4±0.8	-4.1±0.5	0.001
50% Improvement	120, 68.2%	46, 79.3%	74, 57.8%	0.026
Global Symptomatic Status				
Baseline	62.3±1.9	66.5±3.4	60.5±2.3	0.141
Change**	-34.4±2.6	-51.1±4.6	-26.9±2.8	<0.001
50% Improvement	96, 54.9%	42, 77.8%	54, 42.2%	<0.001
AET 4.0%	64, 34.2%	36, 61.0%	28, 21.9%	<0.001
RET 1.4%	103, 55.1%	45, 76.3%	58, 45.3%	<0.001
SI (acid) 50%	36, 19.3%	21, 35.6%	15, 11.7%	<0.001
SI (impedance) 50%	80, 42.8%	40, 67.8%	40, 31.3%	<0.001
SAP (acid) 50%	54, 28.9%	27, 45.8%	27, 21.1%	0.001
SAP (impedance) 50%	89, 47.6%	40, 67.8%	49, 38.3%	<0.001
Total reflux events 48	72, 38.5%	32, 54.2%	40, 31.3%	0.003
Total reflux events 73	28, 15.0%	16, 27.1%	12, 9.4%	0.002
AET + SAP (acid)	26, 13.9%	19, 32.2%	7, 5.5%	<0.001
AET + SAP or SI (acid)	30, 16.0%	21, 35.6%	9, 7.0%	<0.001
RET + SAP (impedance)	56, 29.9%	29, 49.2%	27, 21.1%	<0.001
RET + SAP or SI (impedance)	69, 36.9%	37, 62.7%	32, 25.0%	<0.001
Any reflux evidence (with symptom correlation)	74, 39.6%	41, 69.5%	33, 25.8%	<0.001

AET: acid exposure time; RET: reflux exposure time; SI: symptom index; SAP: symptom association probability assessed by the Ghillebert Probability Estimate; PPI: proton pump inhibitor

* heartburn, acid regurgitation

** between baseline and follow-up assessments

Table 2

Proportions of Patients with Abnormal pH and Impedance Parameters by PPI Status

Parameter	All patients <i>n</i> =187	On PPI <i>n</i> =93	Off PPI <i>n</i> =94	<i>P</i> value
AET 4.0%	64, 34.2%	23, 24.7%	41, 43.6%	0.006
RET 1.4%	103, 55.1%	53, 57.0%	50, 53.2%	0.602
SI (acid) 50%	36, 19.3%	10, 10.8%	26, 27.7%	0.003
SI (impedance) 50%	80, 42.8%	37, 39.8%	43, 45.7%	0.410
SAP (acid) 50%	54, 28.9%	12, 12.9%	42, 44.7%	<0.001
SAP (impedance) 50%	89, 47.6%	32, 34.4%	57, 60.6%	<0.001
Total reflux events 48	72, 38.5%	36, 38.7%	36, 38.3%	0.954
Total reflux events 73	28, 15.0%	14, 15.1%	14, 14.9%	0.976
AET + SAP (acid)	26, 13.9%	6, 6.5%	20, 21.3%	0.005
AET + SAP or SI (acid)	30, 16.0%	9, 9.7%	21, 22.3%	0.027
RET + SAP (impedance)	56, 29.9%	19, 20.4%	37, 39.4%	0.005
RET + SAP or SI (impedance)	69, 36.9%	31, 33.3%	38, 40.4%	0.315
Any reflux evidence (with symptom correlation)	74, 39.6%	33, 35.5%	41, 43.6%	0.255

AET: acid exposure time; RET: reflux exposure time; SI: symptom index; SAP: symptom association probability assessed by the Ghillebert Probability Estimate; PPI: proton pump inhibitor

Table 3

Predictors of dominant symptom intensity (DSI) improvement on univariate analysis, reported as p values from individual comparisons

	Linear DSI change			50% DSI improvement		
	All <i>n</i> =187	Surgical <i>n</i> =59	Medical <i>n</i> =128	All <i>n</i> =187	Surgical <i>n</i> =59	Medical <i>n</i> =128
Acid Parameters						
AET total, %	0.049	0.048	0.936	0.991	0.818	0.372
AET 4.0%	0.006	0.253	0.252	0.559	0.307	0.750
SI (acid) 50%	0.183	0.123	0.357	0.388	0.370	0.647
SAP (acid) >95%	0.239	0.099	0.387	0.528	0.788	0.153
Impedance Parameters						
RET total, %	0.030	0.147	0.814	0.340	0.212	0.307
RET 1.4%	0.957	0.518	0.104	0.299	0.810	0.038
SI (impedance) 50%	0.893	0.394	0.060	0.790	0.375	0.250
SAP (impedance) >95%	0.018	0.160	0.340	0.906	0.962	0.567
Reflux events 48	0.657	0.480	0.373	0.650	0.362	0.087
Reflux events 73	0.139	0.080	0.414	0.562	0.350	0.390

AET: acid exposure time; RET: reflux exposure time; SI: symptom index; SAP: symptom association probability measured by Ghillebert probability estimate; PPI: proton pump inhibitor

Table 4

Predictors of global symptom improvement (GSS) on univariate analysis, reported as p values from individual comparisons,

	Linear GSS change			50% GSS improvement		
	All <i>n</i> =187	Surgical <i>n</i> =59	Medical <i>n</i> =128	All <i>n</i> =187	Surgical <i>n</i> =59	Medical <i>n</i> =128
Acid Parameters						
AET total, %	<0.001	0.025	0.026	0.001	0.290	0.028
AET 4.0%	<0.001	0.278	0.008	0.001	0.406	0.003
SI (acid) 50%	0.167	0.381	0.581	0.098	0.406	0.25
SAP (acid) >95%	0.138	0.108	0.468	0.388	0.826	0.78
Impedance Parameters						
RET total, %	0.001	0.077	0.175	0.011	0.166	0.252
RET 1.4%	0.078	0.181	0.910	0.082	0.300	0.84
SI (impedance) 50%	0.147	0.474	0.96	0.024	0.172	0.68
SAP (impedance) >95%	0.001	0.668	0.008	0.006	0.595	0.06
Reflux events 48	0.130	0.149	0.73	0.144	0.117	0.87
Reflux events 73	0.059	0.148	0.87	0.184	0.339	0.828

AET: acid exposure time; RET: reflux exposure time; SI: symptom index; SAP: symptom association probability measured by Ghillebert probability estimate; PPI: proton pump inhibitor