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Acid-Based Parameters on pH-Impedance Testing Predict Symptom Improvement With Medical Management Better Than Impedance Parameters

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Abstract

OBJECTIVES—pH-impedance testing detects reflux events irrespective of pH, but its value in predicting treatment outcome is unclear. We prospectively evaluated subjects treated medically after pH-impedance testing to determine predictors of symptom improvement.

METHODS—Subjects referred for pH-impedance testing completed questionnaires in which dominant symptoms and global symptom severity (GSS) were recorded. Acid-reflux parameters (acid-exposure time, AET; symptom association by Ghillebert probability estimate, GPE; symptom index, SI) and impedance reflux parameters (reflux-exposure time, RET; number of reflux events; GPE and SI with impedance data) were extracted. Symptoms and GSS were prospectively reevaluated after medical therapy. Univariate and multivariate analyses determined predictors of GSS improvement following medical management.

RESULTS—Over 5 years, 128 subjects (mean 53.3 ± 1.3 years, 66.4% female; typical symptoms 57.0%, 53.9% tested on therapy) underwent pH-impedance testing and subsequent medical therapy for reflux symptoms, and completed required questionnaires. On follow-up 3.35 ± 0.14 years later, mean GSS declined by 45.0%, with 42.2% patients reporting 50% GSS improvement. On univariate analysis, total AET, AET 4.0%, and GPE for all reflux events predicted both linear and 50% GSS improvement, but RET and number of reflux events did not. On multivariate analysis, controlling for testing on or off therapy, only AET ($P = 0.003$) and GPE for all reflux events ($P = 0.029$) predicted GSS improvement.

CONCLUSIONS—Acid-based reflux parameters offer greater value over impedance-based nonacid-reflux parameters in predicting symptomatic responses to proton pump inhibitor (PPI)

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CONFLICT OF INTEREST

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therapy. Our findings support conducting pH-impedance studies off PPI therapy to maximize clinical utility in predicting outcome.

INTRODUCTION

Combined esophageal multichannel intra-luminal impedance and pH monitoring represents a relatively new technology in which serial impedance sensors on a catheter detect changes in resistance (impedance) to electrical current and, consequently, the presence of content or bolus within the esophageal lumen to complement pH monitoring (1). This arrangement determines the direction of esophageal bolus movement (anterograde, as in swallowed bolus, or retrograde, as in reflux), quantification of bolus pH via accompanying pH electrodes, and evaluation of symptom association with reflux episodes (2). As pH-impedance testing detects reflux irrespective of pH, monitoring can be performed in subjects undergoing anti-secretory therapy (3).

In the past decade, studies, consensus reports, and practice guidelines have all suggested that pH-impedance monitoring detects reflux episodes with higher diagnostic sensitivity compared with traditional pH testing alone (4–8). Further, multicenter studies have shown an increased diagnostic yield for detection of non-acid-reflux events when pH-impedance testing is performed on anti-secretory therapy (9–10). Specifically, symptom–reflux association techniques such as the symptom index (SI) and symptom association probability (SAP) have been used to evaluate the temporal relationships between symptoms and detected reflux events (11,12).

However, debate continues as to whether the clinical utility of pH-impedance testing in predicting symptomatic outcome is greater when performed on or off anti-secretory therapy (13–15). This discourse stems partly from the yet unclear clinical significance of non-acid-reflux events on anti-secretory therapy. Nonacid-reflux events are indeed much fewer after anti-reflux surgery (ARS) compared with healthy volunteers (16), and limited data suggest that the presence of symptom–reflux association with nonacid events may predict response to ARS (17–19). However, available literature does not provide concordant guidance on whether testing on or testing off anti-secretory therapy provides better predictive utility, especially for continuing medical management in contrast to ARS.

Therefore, although pH-impedance testing may increase the yield of detecting reflux events and may assist with the selection of patients for ARS, it remains unclear whether or how impedance parameters add value to the predictive power of long-established acid-based parameters. For the purposes of this report, we hypothesized that, as gastroesophageal reflux disease (GERD) is indeed an acid-mediated disease, acid parameters should drive medical management with anti-secretory therapy. We sought to determine whether impedance parameters contribute adjunctive benefits to predicting symptomatic outcomes in the medical management of GERD and, if so, which impedance parameters have the best clinical utility in this regard.

METHODS

Subjects

All adult patients (≥ 18 years) with persistent GERD symptoms despite seemingly adequate anti-secretory therapy referred to the Gastroenterology Motility Center at Washington University in Saint Louis, Missouri, between January 2005 and August 2010 for ambulatory pH-impedance testing were eligible for inclusion. Patients with histopathology-based esophageal motility disorders (e.g., achalasia, scleroderma esophagus), past history of esophageal surgery including fundoplication, and patients with inadequate (defined as poor data quality with significant artifact precluding data analysis) or incomplete (defined as recording time < 14 h) studies were excluded. Consent was obtained from each patient for review of their clinical data and for answering survey questions pertaining to this study. This study protocol was approved by the Human Research Protection Office (Institutional Review Board) at Washington University in Saint Louis.

Data collection

Before pH-impedance testing, all patients completed a subjective symptom survey to characterize their dominant and secondary symptoms as well as their overall symptomatic status. In this symptom survey, symptom frequency and severity are individually rated on five-point Likert scales generated *a priori* for esophageal physiologic tests at our institution; these scales have been used in similar published outcome assessments (20,21). The scale of symptom frequency ranges from 0 (for no symptoms) to 4 (for multiple daily episodes). Similarly, the scale of symptom severity ranges from 0 (for no symptoms) to 4 (for very severe symptoms). Symptom intensity may then be calculated as the product of symptom frequency and symptom severity, with a maximum possible score of 16. In addition, overall global symptom severity (GSS) is recorded on a 100-point visual analog scale.

At our institution, pH-impedance testing is designated as “open access”. Therefore, pH and pH-impedance studies are requested by referring gastroenterologists or surgeons not only for the purposes of quantifying acid exposure and affirming the presence of reflux disease but also for ruling out reflux disease in certain instances; the referring physicians determine whether testing should be performed on or off anti-secretory therapy. To reflect this fact and to address a “real-world” practice pattern, we included both sets of patients, those tested on and those off anti-secretory therapy, in this study. When pH-impedance testing is performed off anti-secretory therapy, patients are required to discontinue anti-secretory therapy at least 7 days prior to the study, and histamine-2 receptor antagonists, prokinetic agents, and antacids at least 3 days prior to the study. All pH-impedance studies are performed after an overnight fast. The pH-impedance catheter (Sandhill Scientific, Highlands Ranch, CO), with six impedance electrodes and one pH sensor, is inserted transnasally with the esophageal pH sensor positioned 5 cm proximal to the manometrically localized lower esophageal sphincter. This catheter configuration allows for monitoring changes in intra-luminal impedance at 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter.

After catheter placement, patients are then instructed to resume their normal daily activities and diet. Each patient is provided a diary to record the timing of meals, activities, and

symptoms. Moreover, patients are instructed to press buttons on an electronic recording device corresponding to symptom events. Approximately 24 h after catheter placement, patients return to the Motility Center for catheter removal. Data are then uploaded into and analyzed with dedicated software (Bioview Analysis; Sandhill Scientific). This software was used to collect and calculate the number of reflux events, exposure times, and symptom–reflux correlation parameters. Automated analysis was used to initially interrogate the pH-impedance studies. Studies were independently evaluated by two investigators (A.P. and C.P.G.), and discordance was resolved by discussion.

Parameters derived from raw pH-impedance data included the acid-exposure time (AET) and the reflux-exposure time (RET). The AET provided a quantitative measure of the time for which esophageal pH remained below 4 in the distal esophagus, expressed as a percentage. A total AET of 4.0% was considered abnormal for the purposes of this study, per our institutional threshold with documented sensitivity (91%) and specificity (85%) for discriminating esophagitis (22). The RET was used as a surrogate quantitative measure of reflux, and was defined as the percentage of time for which refluxate was in contact with the pair of distal esophageal impedance electrodes located adjacent to the esophageal pH sensor 5 cm above the lower esophageal sphincter. For a reflux event to be captured and included in the calculation of the RET, the refluxate needed to be detected in three consecutive distal pairs of impedance electrodes. The RET was then calculated as an aggregate of the amount of time that refluxate remained in contact with the distal impedance electrode, and was reported as a percentage over 24 h. For the purposes of this study, the RET was considered elevated if the value was 1.4%, a threshold which has been validated (23).

For symptom–reflux correlation, only symptoms that occurred within 2 min of a pH- or impedance-detected reflux event were considered. SAP was calculated using the Ghillebert probability estimate as the sum of partial probabilities for the exact numbers of reflux-associated symptoms within the context of the total number of symptoms, taking the total duration of the pH-impedance study and the total exposure time into consideration (24,25). The SAP was considered positive if the likelihood of a chance association between the reflux event and the symptom was <5% (i.e., $P < 0.05$). The SI was calculated as the ratio of reflux-related symptoms to the total number of recorded symptoms, and was considered positive if 50% (26). The SI and SAP were each calculated first with pH-detected acid-reflux events, then recalculated with all impedance-detected reflux events.

Patients with complete demographic, pH-impedance, and symptom data were subsequently prospectively contacted to assess treatment approaches and symptom outcomes. Treatment approaches were implemented by each patient's treating gastroenterologist or surgeon, taking into account the pH-impedance test results, conventional clinical algorithms, and each patient's individual health and personal preferences; these decisions were not influenced or altered by this study. Symptomatic outcomes were assessed by re-administering the pre-procedure symptom survey. The overall symptomatic outcome was quantified as changes in GSS and symptom intensity scores. Subjects tested on and off proton pump inhibitor (PPI) therapy were analyzed separately and results were compared.

Data analysis

Data are reported as the mean $\pm$ standard error of the mean (s.e.m.) unless stated otherwise. Categorical data were compared using the χ^2 -test or Fisher's exact test as appropriate. Grouped data were compared using the two-tailed Student's *t*-test. Univariate and multivariate analyses were performed to identify findings that predicted an improved symptomatic outcome, measured as both linear GSS change and 50% GSS improvement upon follow-up. Linear regression models were created to determine predictors of a successful symptomatic outcome with medical management, controlling for the use of anti-secretory therapy during testing, and included clinical demographic data as well as all traditional acid and impedance parameters as variables since these parameters tend to be linked as covariates. In all cases, $P < 0.05$ was required for statistical significance. All statistical analyses were performed using IBM SPSS Statistics V.21.0 (Armonk, NY).

RESULTS

Interrogation of the pH-impedance database revealed 302 patients who underwent ambulatory pH-impedance testing for GERD symptoms during the 5-year study period. A total of 60 patients did not meet inclusion criteria (7 had inadequate or incomplete studies, 3 had histopathology-based esophageal motility disorders, 26 had prior fundoplication or other esophageal surgery, and 24 were missing pre-procedure symptom surveys), 59 patients were managed surgically, 53 could not be contacted for follow-up, and 2 declined to participate; these subjects were excluded. The remaining 128 subjects (53.3 ± 1.3 years, 66.4% female, 82.8% Caucasian) underwent medical therapy for reflux symptoms, fulfilled study inclusion criteria, were successfully contacted by telephone, consented to participate in the study, and constituted the study sample.

Typical reflux symptoms were reported by 73 (57.0%) patients (38 with heartburn, 35 with regurgitation), whereas the remaining 55 (43.0%) presented with atypical symptoms (15 with chest pain, 37 with cough, 2 with hoarseness, 1 with throat clearing). Testing was performed off anti-secretory therapy in 46.1% patients and on therapy in 53.9%; these two groups were each analyzed separately below and represented our two primary groups for comparison. There were no differences in demographic or clinical parameters, baseline symptom intensity, or baseline GSS between these two subsets ($P = 0.136$ for each comparison, Table 1).

Collectively, 21.9% of patients had an abnormal AET and 45.3% had an abnormal RET (Table 2). Reported symptoms and number of acid-reflux events were significantly higher when testing was performed off anti-secretory therapy (Figure 1). Number of reflux events detected by impedance was significantly higher than that detected by pH monitoring, as expected. Consequently, symptom-reflux association was proportionately higher with impedance-detected reflux events compared with acid-detected reflux events (SI: 31.3 vs. 11.7%, respectively, $P < 0.001$; SAP: 38.3 vs. 21.1%, respectively, $P = 0.003$; Figure 1). A significantly higher proportion demonstrated symptom-reflux correlation (as assessed by Ghillebert probability estimate) in patients tested off PPI, with both acid-reflex events ($P < 0.001$) and all reflux events detected by impedance ($P = 0.028$). Proportions of patients with other acid and impedance parameters did not differ between subjects tested on and those

tested off anti-secretory therapy, with $P = 0.09$ for each comparison (Table 2). However, there were more subjects with abnormal AET in the cohort tested off PPI (28.8% compared with 15.9% on PPI, $P = 0.09$). Proportions with concordance between abnormal AET and acid-based reflux–symptom association, and abnormal RET and impedance-based reflux–symptom association also were similar in these two subsets.

At the end of 3.35 ± 0.14 years of follow-up, mean GSS collectively improved from a baseline of 60.4 ± 2.3 to 33.2 ± 2.3 , a decline of 45.0%. Dominant symptom intensity improved from 8.4 ± 0.5 to 4.3 ± 0.4 , a decrease of 48.8%. Overall, 54 (42.2%) subjects reported a GSS improvement of $\geq 50\%$, and 74 (57.8%) subjects reported an improvement in dominant symptom intensity $\geq 50\%$. Mean GSS improvement was not different between cohorts tested on or off anti-secretory therapy ($P = 0.529$); however, there was a trend toward higher rates of $\geq 50\%$ GSS improvement in subjects tested off anti-secretory therapy ($P = 0.066$; Table 1). Mean GSS improvement tended to be better with atypical symptoms (-32.4 ± 4.4) compared with typical symptoms (-22.6 ± 3.7) with a nonsignificant trend ($P = 0.085$); atypical symptom presentation was significantly associated with a higher rate of $\geq 50\%$ improvement in GSS ($P = 0.027$; Table 3). GSS improvement was similar between patients with elevated AET detected off therapy and on therapy (-42.8 ± 9.1 vs. -38.0 ± 8.4 , respectively, $P = 0.72$); change in dominant symptom intensity was also similar (-5.8 ± 1.5 vs. -4.7 ± 1.7 , $P = 0.66$).

All patients

On univariate analysis, acid parameters were significantly associated with linear GSS improvement. Both total AET as a continuous variable ($P = 0.026$) and abnormal AET above 4.0% ($P = 0.008$) significantly predicted GSS improvement in our study population. However, neither SI nor SAP calculated with acid-reflux events predicted GSS improvement. Among impedance parameters, only SAP calculated with impedance-detected reflux events significantly predicted GSS improvement ($P = 0.008$); RET above 1.4%, RET as a continuous variable, SI for all reflux events, and thresholds for total number of reflux events (either 73 or 48 reflux events) did not. Univariate analysis assessing predictors of $\geq 50\%$ GSS improvement demonstrated total AET ($P = 0.028$), AET $\geq 4.0\%$ ($P = 0.003$), and SAP for all reflux events ($P = 0.061$) as significant predictors (Table 4).

On multivariate analysis controlling for PPI status, only AET $\geq 4.0\%$ ($P = 0.003$) and SAP calculated for all reflux events ($P = 0.029$) predicted linear GSS improvement, whereas age, gender, anti-secretory therapy, typical symptom presentation, RET $\geq 1.4\%$, SAP calculated for acid-reflux events, and established thresholds for total numbers of reflux events (48 off therapy, 73 on therapy) did not ($P = 0.17$ for all). For $\geq 50\%$ GSS improvement, only atypical symptom presentation ($P = 0.021$) and AET $\geq 4.0\%$ ($P = 0.003$) represented significant predictors (Figure 2).

Testing on PPI

The 69 subjects who underwent testing on anti-secretory therapy were further analyzed. On univariate analysis assessing predictors of linear GSS change, only positive SAP for all reflux events significantly predicted GSS improvement ($P = 0.011$), although other acid and

impedance parameters did not ($P = 0.11$ for all). Moreover, only AET $\geq 4.0\%$ predicted $\geq 50\%$ GSS improvement on univariate analysis ($P = 0.049$), whereas other acid and impedance parameters did not ($P = 0.22$ for all; Table 4).

On multivariate analysis evaluating predictors of linear GSS improvement, only AET $\geq 4.0\%$ represented a significant predictor ($P = 0.02$), while impedance SAP trended toward significance ($P = 0.06$), but other clinical characteristics and testing parameters did not ($P = 0.15$ for all, Figure 2). Also, on multivariate analysis, only AET $\geq 4.0\%$ significantly predicted $\geq 50\%$ GSS improvement ($P = 0.02$), whereas atypical symptom presentation again trended toward significance ($P = 0.07$), and other parameters did not reach significance ($P = 0.16$ for all).

Testing off PPI

Similarly, the 59 subjects who underwent testing off anti-secretory therapy were analyzed separately. On univariate analysis, only total AET significantly predicted linear GSS improvement ($P = 0.04$), while abnormal AET above 4.0% strongly trended toward doing so ($P = 0.05$), but other acid and impedance parameters did not reach significance ($P = 0.21$ for all). Moreover, total AET ($P = 0.10$) and AET $\geq 4.0\%$ ($P = 0.06$) trended toward predicting $\geq 50\%$ GSS improvement on univariate analysis (Table 4).

On multivariate analysis of these subjects tested off anti-secretory therapy, only AET $\geq 4.0\%$ significantly predicted linear GSS improvement ($P = 0.02$), while established thresholds for total numbers of reflux events trended toward significance ($P = 0.05$, Figure 2). Also on multivariate analysis, AET $\geq 4.0\%$ ($P = 0.02$) and thresholds for total numbers of reflux events ($P = 0.03$) represented predictors of $\geq 50\%$ GSS improvement, although other parameters did not ($P = 0.24$ for all).

DISCUSSION

In this study, we demonstrate that acid-based reflux parameters have higher clinical utility compared with commonly used impedance-based non-acid-reflux parameters in predicting response to PPI therapy. Specifically, our univariate and multivariate analyses demonstrate that total AET and abnormal AET $\geq 4.0\%$ predict symptomatic improvement with anti-secretory therapy to far greater degrees than total RET, abnormal RET $\geq 1.4\%$, and total numbers of reflux events. Impedance testing provided most gain in detecting reflux events, consequently leading to higher proportions with symptom–reflux correlation, a parameter that also predicted symptom outcome. Given the higher rates of detection of symptom–reflux correlation on patients tested off anti-secretory therapy, our findings support performing pH-impedance studies off PPI therapy to maximize clinical gain in predicting subjects who may benefit from medical management.

Acid parameters represent an established approach to predicting outcomes in GERD (27). For instance, increased acid reflux correlates with the presence of Barrett's esophagus, a long-term consequence of GERD in predisposed individuals; total AET correlates with the length of Barrett's esophagus (28). As the numeric total AET value increases, the likelihood of a higher grade along the GERD spectrum (no esophagitis, esophagitis, uncomplicated

Barrett's esophagus, complicated Barrett's esophagus) also increases (29). Symptomatic GERD patients with abnormal acid exposure and/or symptom–reflux association respond more favorably to PPI therapy than those with normal acid exposure and lack of symptom–reflux correlation on pH testing (30). Acid-reflux parameters also predict successful outcome after ARS (31), whereas normal preoperative pH testing predicts suboptimal subjective outcome (32). Therefore, there is ample evidence supporting the utility of acid-driven parameters in predicting outcomes in the management of GERD, a concept that is at the core of our findings in this study.

In contrast, impedance-driven outcome data are limited, despite the fact that symptom–reflux correlation benefits from the use of pH-impedance testing. Our results concur with those in the literature in that impedance monitoring detects more reflux events than pH monitoring. Although previous assessments suggest that the clinical value and optimal use of symptom–reflux correlation remain unclear (33,34), we demonstrate that SAP from impedance testing is an independent predictor of symptomatic outcome after medical therapy of GERD. Despite this finding, only limited outcome data exist to suggest a relationship between non-acidic reflux detected by impedance testing and symptoms in suspected GERD (35). The clinical significance of these reflux events must be carefully evaluated in the appropriate context (36). Although the pH portion of the pH-impedance study and symptom–reflux correlation can provide direction regarding significance of impedance-detected reflux events, this can only be augmented by performing the study off PPI therapy. Further, it is unclear as to how to evaluate pH findings in patients on PPI therapy, unless values are clearly abnormal. Varying thresholds have been utilized to designate abnormality, but the clinical outcome from use of these thresholds remains unclear (14,27,37). The higher rates of symptom–reflux correlation detected by impedance testing could also be subject to over interpretation, especially in the setting of lower frequencies of reflux events (38). Taking all these factors and our findings into consideration, impedance monitoring has the potential to complement pH-detected reflux events and participate in predicting outcome. However, recognition of both pH- and impedance-detected reflux events, and, particularly, reporting of symptom events, requires testing to be performed off therapy (39).

In this study, we evaluated the value of a cumulative bolus contact time metric to correspond to the AET, measured at the same level 5 cm proximal to the lower esophageal sphincter, which we have termed the reflux-exposure time, or RET. This metric has been evaluated in normal volunteers, with normal thresholds determined (23). It is well known that reflux durations measured by impedance are shorter than corresponding pH-determined reflux durations, because mucosal acidification persists despite clearance of the refluxate (23,40). Therefore, impedance-detected reflux events are brief, and symptom correlation with these brief events could be more specific in symptom–reflux association testing. Further, refluxates could generate symptoms by mechanical stretch and not just chemical stimulation, which may not trigger correlation with a pH-detected reflux event. Hence, impedance-driven symptom–reflux testing holds potential for added clinical value. Our data suggest that there is benefit in symptom–reflux association testing when pH data is supplemented with impedance data, indicating that pH-impedance monitoring clearly has a clinical role in reflux testing.

However, acid parameters drive management, as acid suppression remains the cornerstone of GERD therapy (41,42). Despite the fact that reflux of gastric contents continues despite acid suppression, most patients have adequate symptom relief from medical management with acid suppressants. Therefore, acid parameters intuitively drive symptom outcome from medical management, and it follows that the predictive value of testing subjects off anti-secretory therapy would be higher compared with those on therapy, as the diagnostic yield is much higher off therapy. In recent years, baclofen, a gamma amino butyric acid B receptor agonist, has been implemented as an adjunct to reduce the frequency of reflux events to complement anti-secretory therapy (43–45). This agent could potentially augment medical management of reflux and improve symptomatic outcomes by reducing reflux events; however, baclofen was not utilized for medical management in our study cohort.

The strength of our conclusions is tempered by several limitations. Patients were identified retrospectively, although data were collected prospectively; some did not complete symptom assessments at the time of the pH-impedance study, and others could not be contacted for assessment of treatment response. Follow-up symptom scores, especially global symptom scores, could have been affected by other non-reflux processes including functional pain, which we did not evaluate. We did not have a comparator control group with only pH testing, which could have revealed differences between pH and pH-impedance monitoring; nor did we have a cohort treated with ARS, which could have put the response to medical therapy into perspective. We could not accurately assess PPI compliance at follow-up, nor reliably determine how many subjects had been treated with different forms of adjunctive medical therapy for subgroup analyses. Our results demonstrated only a statistical trend in proportions of patients with abnormal AET off PPI compared with those tested on PPI, which reflects the fact that many with markedly abnormal AET (in the off PPI cohort) were likely triaged to ARS and did not fulfill inclusion criteria.

Moreover, therapy following pH-impedance monitoring was not protocolized; instead, management was left to the ordering physicians, who may or may not have used accepted guidelines in planning therapeutic options. It is also not clear why many patients with normal pH-impedance parameters and off PPI were left on anti-secretory therapy by their treating physicians, but this reflects real-world practice and contributes to overuse of PPIs. Finally, we had a higher proportion of atypical reflux symptoms in this cohort, likely driven by the open-access favoring of pH-impedance monitoring for atypical reflux symptoms in the early years of pH-impedance testing. We believe this is the likely explanation for trends suggesting better prediction of symptom improvement with atypical symptoms rather than typical symptoms, as standard pH monitoring without impedance was being performed more commonly to document abnormal esophageal pH patterns for typical reflux symptoms at that time frame. Nevertheless, we believe that our results reflect a representative assessment of how pH-impedance monitoring studies are used in the real world, and despite these limitations, our results can help provide a starting point for planning patient management, and especially for planning future studies.

In summary, acid-based reflux parameters have clinical utility in predicting a symptomatic response to anti-secretory therapy, whereas impedance parameters can complement acid monitoring in the detection of clinically relevant symptom–reflux association. Abnormal

acid-based reflux parameters can predict symptom improvement with medical management better than impedance-based reflux parameters. As abnormal acid-based parameters are detected more often off anti-secretory therapy, we conclude that pH-impedance testing off PPI therapy has both diagnostic and management implications when the medical management of reflux disease is planned. Future studies need to utilize protocolized medical and surgical therapy to better evaluate the implications of pH-impedance testing.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ pH-impedance testing identifies reflux events irrespective of pH.
- ✓ Acid suppression converts acidic pH reflux into non-acidic or weakly acidic pH events.
- ✓ Acid-based pH parameters predict symptom improvement with anti-reflux surgery.
- ✓ Impedance-detected reflux events decrease following anti-reflux surgery.

WHAT IS NEW HERE

- ✓ Acid-based pH parameters have a stronger predictive value for symptom improvement with medical management compared with impedance-based reflux parameters.
- ✓ Impedance parameters complement, but do not replace, acid-based pH parameters.
- ✓ Symptom–reflux correlation is detected more frequently when testing is performed off acid suppression.
- ✓ pH-impedance testing performed off proton pump inhibitor therapy provides maximal clinical utility.

Figure 1.

Symptoms, reflux events, and symptom–reflux correlation. Reported symptoms and frequency of acid reflux events were significantly higher when testing was performed off proton pump inhibitor (PPI) therapy (* $P = 0.04$). Frequency of reflux events detected by impedance (all reflux events) was similar whether testing was performed on or off PPI therapy ($P = 0.26$). Both symptom index (SI) and symptom association probability (SAP) were proportionately more frequent with impedance-detected reflux events (** $P = 0.002$).

Dependent variables		Outcome variable		
		<u>Linear GSS change</u> <i>Risk ratio (95% CI)</i>		
		All patients	Off PPI	On PPI
Age				
Gender				
Atypical symptoms				
<u>Acid parameters</u>				
Abnormal AET	21.9 (7.8–35.9)*	31.5 (6.2–56.8)**	24.1 (3.4–44.8)**	
SAP acid reflux				
<u>Impedance parameters</u>				
Abnormal RET				
SAP all reflux	18.2 (1.9–34.6) [#]			
Number of reflux events				

Figure 2.

Multivariate analysis showing independent predictors of symptomatic outcome after medical management, as measured by linear change in global symptom score (GSS). Abnormal AET 4.0% was an independent predictor in multivariate analysis controlling for PPI status (* $P = 0.003$), as well as in separate multivariate analysis of patients on and off PPI (** $P = 0.02$). Positive symptom association probability (SAP) from impedance-detected reflux events predicted linear GSS change (# $P = 0.03$), but this did not hold up on separate multivariate analysis on and off PPI in this model. AET, acid exposure time, CI, confidence intervals; PPI, proton pump inhibitor; RET, reflux exposure time.

Table 1

Demographics and clinical characteristics

	All subjects (n=128)	Tested on PPI (n=69)	Tested off PPI (n=59)	P value
Mean age (year)	53.3±1.3	53.2±1.6	53.4±2.0	0.92
Sex (female)	85, 66.4%	48, 69.6%	37, 62.7%	0.46
Race (Caucasian)	106, 82.8%	56, 81.2%	50, 84.7%	0.50
Typical symptoms ^a	73, 57.0%	38, 55.1%	35, 59.3%	0.72
Duration of follow-up (months)	40.2±1.7	42.5±2.2	37.5±2.5	0.14
<i>Symptom intensity</i>				
Baseline	8.4±0.5	8.6±0.7	8.2±0.7	0.73
Change ^b	−4.1±0.5	−4.2±0.8	−4.1±0.8	0.98
50% Improvement	74 (57.8%)	38 (55.1%)	36 (61.0%)	0.57
<i>Global symptomatic status</i>				
Baseline	60.4±2.3	62.4±3.1	58.1±3.4	0.34
Change ^b	−26.9±2.8	−25.2±3.5	−28.8±4.6	0.53
50% Improvement	54 (42.2%)	24 (34.8%)	30 (50.8%)	0.07

PPI, proton pump inhibitor.

^a Heartburn, acid regurgitation.

^b Between baseline and follow-up assessments.

Table 2

Proportions of patients with abnormal pH and impedance parameters

Parameter	All patients (n=128)	On PPI (n=69)	Off PPI (n=59)	P value
AET 4.0%	28 (21.9%)	11 (15.9%)	17 (28.8%)	0.09
RET 1.4%	58 (45.3%)	33 (47.8%)	25 (42.4%)	0.60
SI (acid) 50%	15 (11.7%)	5 (7.2%)	10 (16.9%)	0.10
SI (impedance) 50%	40 (31.3%)	19 (27.5%)	21 (35.6%)	0.35
SAP (acid) 50%	27 (21.1%)	6 (8.7%)	21 (35.6%)	<0.001
SAP (impedance) 50%	49 (38.3%)	20 (29.0%)	29 (49.2%)	0.03
Total reflux events 48	40 (31.3%)	24 (34.8%)	16 (27.1%)	0.45
Total reflux events 73	12 (9.4%)	8 (11.6%)	4 (6.8%)	0.38
Acid SAP + AET	7 (5.5%)	2 (2.9%)	5 (8.5%)	0.25
Acid (SAP or SI) + AET	9 (7.0%)	3 (4.3%)	6 (10.2%)	0.30
All SAP + RET	27 (21.1%)	11 (15.9%)	16 (27.1%)	0.13
All (SAP or SI) + RET	32 (25.0%)	15 (21.7%)	17 (28.8%)	0.42

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

Table 3

Symptom improvement by symptom presentation

	All subjects (n=128)	Typical Sx (n=73)	Atypical Sx (n=55)	P value
<i>Symptom intensity</i>				
Baseline	8.4±0.5	7.4 0.7	9.8 0.7	0.02
Change ^a	-4.1±0.5	-3.1 0.7	-5.7 0.8	0.02
50% Improvement	74 (57.8%)	39 (53.4%)	35 (63.6%)	0.44
<i>Global symptomatic status</i>				
Baseline	60.4±2.3	57.6 3.0	64.1 3.4	0.15
Change ^a	-26.9±2.8	-22.6 3.7	-32.4 4.4	0.09
50% Improvement	54 (42.2%)	24 (32.9%)	30 (54.5%)	0.03

Typical symptoms: heartburn, acid regurgitation; atypical symptoms: chest pain, cough, other.

^aFrom baseline to follow-up.

Table 4

Predictors of global symptom improvement by univariate analysis, reported as *P* values from individual comparisons

	Linear GSS change			50% GSS improvement		
	All (n=128)	On PPI (n=69)	Off PPI (n=59)	All (n=128)	On PPI (n=69)	Off PPI (n=59)
<i>Acid parameters</i>						
AET total, %	0.03	0.21	0.04	0.03	0.24	0.10
AET 4.0%	0.01	0.11	0.05	0.003	0.049	0.06
SI (acid) 50%	0.58	0.45	0.78	0.25	0.44	0.70
SAP (acid) 50%	0.47	0.52	0.47	0.78	0.31	0.61
<i>Impedance parameters</i>						
RET total, %	0.18	0.23	0.21	0.25	0.22	0.29
RET 1.4%	0.91	0.83	0.75	0.84	0.49	0.47
SI (impedance) 50%	0.96	0.36	0.94	0.68	0.75	0.87
SAP (impedance) 50%	0.008	0.01	0.23	0.06	0.24	0.35
Total reflux events 48	0.73	0.58	0.91	0.87	0.85	0.87
Total reflux events 73	0.87	0.57	0.42	0.82	0.40	0.32

AET, acid exposure time; GSS, global symptomatic status; PPI, proton pump inhibitor; RET, reflux exposure time; SAP, symptom association probability measured by Ghillebert probability estimate; SI, symptom index.