TITLE:

Analyses of the Post-reflux Swallow-induced Peristaltic Wave Index and Nocturnal Baseline Impedance Parameters Increase the Diagnostic Yield of Impedance-pH Monitoring of Patients With Reflux Disease

AUTHORS:

Marzio Frazzoni[1], Edoardo Savarino[2], Nicola de Bortoli[3], Irene Martinucci[3], Manuele Furnari[4], Leonardo Frazzoni[1], Vincenzo Giorgio Mirante[1], Helga Bertani[1], Santino Marchi[3], Rita Conigliaro[1], and Vincenzo Savarino[4].

AFFILIATIONS:

1 Digestive Pathophysiology Unit and Digestive Endoscopy Unit, Baggiovara Hospital, Modena, Italy;

2 Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy;

3 Department of Translational Research and New Technology in Medicine and Surgery, University of Pisa, Pisa, Italy;

4 Gastroenterology Unit, Department of Internal Medicine, University of Genova, Genova, Italy

CORRESPONDING AUTHOR

Marzio Frazzoni, MD, Fisiopatologia Digestiva, Ospedale Baggiovara, Viale Giardini 1355, 41100 Modena, Italy.

e-mail: marziofrazzoni@gmail.com; fax: 0039-59-3961201.

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Abbreviations used in this paper: AUC, area under the curve; EAET, esophageal acid exposure time; ERD, erosive reflux disease; GERD, gastroesophageal reflux disease; MNBI, mean nocturnal baseline impedance; NERD, nonerosive reflux disease; PSPW, post-reflux swallow induced peristaltic wave; ROC, receiver operating characteristic; SAP, symptom association probability; SI, symptom index.

ABSTRACT

BACKGROUND & AIMS: Analyses of impedance parameters such as the post-reflux swallow-induced peristaltic wave (PSPW) index and the mean nocturnal baseline impedance (MNBI) have been proposed to increase the accuracy of diagnosis of reflux disease. We assessed whether these improve the diagnostic yield of impedance pH monitoring of reflux disease.

METHODS: We performed a prospective study of consecutive patients with proton pump inhibitor–responsive heartburn who underwent 24-hour impedance pH monitoring at hospitals in Italy from January 2011 through December 2013. Reviewers blindly analyzed off-therapy impedance pH tracings from 289 patients with proton pump inhibitor–responsive heartburn, 68 with erosive reflux disease and 221 with non-erosive reflux disease (NERD), along with 50 healthy individuals (controls). The PSPW index, the MNBI, the esophageal acid exposure time, the number of total refluxes, and the bolus exposure were calculated, as well as the symptom association probability (SAP) and the symptom index (SI).

RESULTS: In receiver operating characteristic analysis, the area under curve of the PSPW index (0.977; 95% confidence interval, 0.961L0.993) was significantly greater than that of the other impedance pH parameters in identifying patients with reflux disease ($P < .001$). The PSPW index and the MNBI identified patients with erosive reflux disease with the highest level of sensitivity (100% and 91%, respectively), as well as the 118 pH-positive (99% and 86%) and 103 pH-negative (77% and 56%) cases of NERD. The PSPW index and the MNBI identified pH negative NERD with the highest level of sensitivity; values were 82% and 52% for the 65 SAP positive and/or SI-positive cases and 68% and 63% for the 38 SAP-negative and SI-negative cases. Diagnoses of NERD were confirmed by pH-only criteria, including those that were positive on the basis of the SAP or SI, for 165 of 221 cases (75%) and by impedance pH criteria for 216 of 221 cases (98%) (P [.001).

CONCLUSIONS: The PSPW index and the MNBI increase the diagnostic yield of impedance pH monitoring of patients with reflux disease. Analysis of impedance pH data by calculating the PSPW index and the MNBI can increase the accuracy of diagnosis of patients with reflux disease, compared with pH-only data.

Keywords: ROC AUC; Esophageal Chemical Clearance; Esophageal Baseline Impedance; Impedance pH Monitoring; Heartburn; GERD.

INTRODUCTION

Heartburn is the cardinal symptom of gastroesophageal reflux disease (GERD) but can also be reflux unrelated. In uninvestigated patients, symptomatic response to proton pump inhibitor (PPI) therapy may be sufficient to confirm GERD diagnosis without further diagnostic testing.1,2 Indeed, many patients with PPI-responsive heartburn become PPI-dependent, and some of them ask to be rendered free from PPI therapy by surgical or endoscopic interventions; in these cases, diagnosis of GERD must be objectively confirmed before invasive antireflux procedures.1,2 On the other hand, when heartburn persists despite PPI therapy, the diagnosis of GERD is in doubt, and objective evaluation is required.1,2 Normal findings are detected at endoscopy in the vast majority of patients, and reflux monitoring is then indicated. Besides the traditional parameter of percentage esophageal acid exposure time (EAET), a positive symptom-reflux association has been proposed to define hypersensitive esophagus, a clinical entity to be included within the realm of GERD3; for this purpose, the symptom association probability (SAP) and the symptom index (SI) are most commonly used. Currently, impedance-pH monitoring is regarded as the most complete direct reflux test because it allows a full assessment of all reflux episodes, independent of their acidity.4

Studies have shown a positive association of heartburn with weakly acidic refluxes in several patients, thus increasing the proportion of cases with hypersensitive esophagus.5,6 Unfortunately, it is well-recognized that there is a day-to-day variability in symptom perception so that many patients do not have symptoms during a 24-hour test. Moreover, symptom-reflux indexes depend on patient's accuracy in symptom recording, which is often suboptimal; therefore, a diagnosis based on the positivity of a symptom-reflux association index cannot be considered as truly objective but mainly patient-centered.

Recently, the diagnostic accuracy of SAP and SI has been questioned, and it has been claimed that SAP/SI positivity can be overinterpreted, particularly in patients with low rates of reflux, ie, those in whom there is the greatest diagnostic uncertainty.7 Quantitative impedance-pH parameters to be used in conjunction with symptom-reflux association indexes are warranted to improve our ability to diagnose GERD. Recently, 2 novel impedance parameters evaluating esophageal chemical clearance and mucosal integrity, namely the post-reflux swallow-induced peristaltic wave (PSPW) index8 and the mean nocturnal baseline impedance (MNBI),9 have been proposed. After a reflux episode, esophageal clearance is primarily achieved by secondary peristalsis removing around 90% of the refluxate and elicited by stretch receptors in the esophageal lining (volume clearance); however, neutral esophageal pH is restored only after a voluntary swallow elicited by an esophago-salivary reflex mediated through vagal afferents and delivering salivary bicarbonate (chemical clearance).10,11 The PSPW index allows assessment of chemical clearance after acidic as well as

weakly acidic refluxes and is then suitable for evaluation of patients off as well as on PPI therapy; lower values have been found in erosive reflux disease (ERD) than in non-erosive reflux disease (NERD), and they are both significantly lower than in functional heartburn.8 Low baseline impedance indicates impairment of mucosal integrity, even in the absence of macroscopic damage.12

Taking into account that nocturnal sleep is less affected by swallows and refluxes, we have recently developed an easy-to-calculate parameter that assesses baseline impedance, ie, the mean nocturnal baseline impedance (MNBI)9; it consists of the mean of three 10-minute nighttime periods, which accurately reflects the 6-hour nocturnal bedtime period, and appears promising in distinguishing hypersensitive esophagus from functional heartburn.9 According to preliminary results,8,9 the PSPW index and the MNBI appear as potentially useful for GERD diagnosis. Our aim was to assess their diagnostic accuracy by evaluating a multicenter case-series of patients with PPI-responsive heartburn who had undergone off therapy impedance-pH monitoring.

METHODS

After study approval by institutional review boards, data prospectively collected at the 4 centers participating in the study were reviewed. Consecutive patients with PPI-responsive heartburn, who were referred to our centers for possible surgical or endoscopic antireflux procedures and who underwent 24-hour impedance-pH monitoring between January 2011 and December 2013, were considered for the study. All patients signed a consent form before undergoing clinical investigations.

A 6-month history of recurrent troublesome heartburn graded according to a validated13 four-grade, Likert-type scale scoring system and repeatedly abolished by 4-week PPI courses (PPI-dependent heartburn), constituted the inclusion criterion. Previous endoscopy performed at least 4 weeks after PPI washout was required. Sjogren syndrome, previous esophagogastric surgery, and referral for chest pain or extraesophageal syndromes constituted exclusion criteria.

Impedance-pH monitoring was preceded by esophageal manometry after PPI withdrawal lasting for at least 2 weeks. Achalasia, scleroderma esophagus, but not esophageal hypomotility (at least 50% pressure waves <30 mm Hg in the distal esophagus) constituted exclusion criteria. The catheter adopted allowed monitoring changes in intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm and in intraluminal pH 5 cm, respectively, above the manometrically defined lower esophageal sphincter.

All tracings were blindly reanalyzed in a random order by expert observers who were rendered unaware of previous analysis results. A dedicated software program (BioView Analysis, Sandhill Scientific, Inc, Highland Ranch, CO) was used in conjunction with a 2-minute time window visual

analysis, with zooming when deemed necessary. Data analysis was performed on liquid and mixed (liquid-gas) reflux episodes for acid (nadir pH <4), weakly acidic (nadir pH between 4 and 7), and weakly alkaline refluxes (nadir pH not below 7) (mealtimes excluded). The time period with esophageal pH < 4, ie, the percentage EAET, the number of total refluxes, and the percentage bolus exposure, were calculated. A positive SAP was defined by 95% or more of symptoms associated with reflux, and a positive SI was defined by 50% or more of symptoms associated with reflux.14 Patients who did not record symptoms during the study or with both SAP <95% and SI <50% were considered as SAP/SI negative. A PSPW was defined as an antegrade 50% drop in impedance relative to the pre-swallow baseline originating in the most proximal impedance site, reaching all the distal impedance sites, and followed by at least 50% return to the baseline in the distal impedance sites (bolus exit) (Figure 1).8 Post-reflux swallows that did not reach the distal impedance sites or occurring more than 30 seconds after the end of reflux episodes were not taken into account. For each impedance-pH tracing, the number of refluxes followed within 30 seconds by a PSPW was divided by the number of total refluxes (manual calculation) to obtain the PSPW index.8 MNBI was assessed from the most distal impedance channel during nighttime recumbent period. Three 10-minute time periods (around 1:00 AM, 2:00 AM, and 3:00 AM) were selected, and the mean baseline for each period was computed with the aid of the software. Time periods including swallows, refluxes, and pH drops were avoided.

The mean of the 3 measurements was manually calculated to obtain the MNBI.9 According to endoscopic findings, patients were subdivided into ERD and NERD. NERD patients were then subdivided according to the percentage EAET into pH-positive NERD and pH-negative NERD; the latter was further subdivided into SAP/SI positive and SAP/SI negative pH-negative NERD. The threshold EAET value used to define pH-positive NERD was based on our receiver operator characteristic (ROC) analysis.To evaluate interobserver reproducibility, 30 tracings, 16 from the pH-positive NERD group and 14 from the pH-negative NERD group, were assessed by 2 independent observers.

Statistics

To analyze the differences among ERD, NERD, and healthy controls, analysis of variance for continuous variables and c2 test for categorical variables were used with Bonferroni correction for multiple comparisons (significance for $P < .05$). For each impedance-pH parameter the overall ability to diagnose GERD was assessed by means of ROC analysis with calculation of the area under the curve (AUC) and pairwise comparisons. The value that maximized the sum of sensitivity and

specificity was considered the best cutoff and was used to calculate sensitivity, specificity, positive and negative predictive values, and overall accuracy. Correlation between PSPW index and MNBI was assessed with Pearson coefficient. Interobserver agreement was evaluated by using the Spearman rank correlation test. A percentage of concordance between PSPW index and MNBI within the GERD subgroups was calculated as (Number of abnormal results by both methods/Number of abnormal results by at least one method) x 100.

RESULTS

Impedance-pH tracings from 289 patients with PPI-dependent heartburn referred to our centers between January 2011 and December 2013 and from 50 healthy controls were analyzed. The main baseline characteristics and impedance-pH findings of patients and controls are reported in Table 1. The PSPW index and the MNBI could be calculated in all 339 tracings and were significantly lower in ERD (68 cases, 10 with grade C/D, 20 with grade B, 38 with grade A reflux esophagitis) than in NERD and in both as compared with healthy controls.

Overall Diagnostic Efficacy of Post-reflux Swallow-induced Peristaltic Wave Index and Mean Nocturnal Baseline Impedance.

Concerning the overall ability to diagnose GERD, according to ROC analysis, the AUC was 0.884 (95% confidence interval, 0.843–0.926) for the EAET; the best cutoff value maximizing the sum of sensitivity and specificity was 3.2% and was used as the threshold to separate pH-positive NERD from pH-negative NERD. The AUC for the number of total refluxes was 0.866 (95% confidence interval, 0.816–0.916) (best cutoff value 48). The AUC for bolus exposure was 0.844 (95% confidence interval, 0.785–0.902) (best cutoff value 1.9%). The AUC for the PSPW index was 0.977 (95% confidence interval, 0.961–0.993) (best cutoff value 61%). The AUC for the MNBI was 0.876 (95% confidence interval, 0.833–0.918) (best cutoff value 2292 ohms). The AUC for the PSPW index was significantly greater than that of all the other impedance-pH parameters ($P < .001$) (Figure 2). The correlation between PSPW index and MNBI was 0.657 ($P < .001$). Concerning interobserver agreement, the Spearman rank correlation was 0.829 (P ¼ .001) for the PSPW index and 0.959 (P ¼ .001) for the MNBI.

Diagnostic Yield of Post-reflux Swallow induced Peristaltic Wave Index and Mean Nocturnal Baseline Impedance in Gastroesophageal Reflux Disease Subgroups

The PSPW index and the MNBI showed the highest sensitivity in GERD patients as subdivided into ERD and NERD (Table 2); concordance between the 2 methods was 91% and 66%, respectively. Eleven of 68 ERD patients (16%) were SAP/SI negative. The diagnostic accuracy of impedance parameters in 118 pH-positive NERD patients and 103 pH-negative NERD patients is reported in Table 3. The PSPW index and the MNBI showed the highest sensitivity and overall accuracy; concordance between the 2 methods was 87% and 42%, respectively. In the pH-negative NERD group, 65 cases were SAP/SI positive, and 38 cases were SAP/SI negative (Table 4). Again, the PSPW index and the MNBI showed the highest sensitivity and overall accuracy; concordance between the 2 methods was 40% and 45%, respectively.

In SAP/SI negative cases, abnormal results were found only with the PSPW index and the MNBI; at least 1 of the 2 was abnormal in 33 of 38 cases (16%) cases, 9 and 7 of whom with an abnormal PSPW index or an abnormal MNBI only, respectively.

Diagnostic Yield of Impedance-pH Versus pH-only Criteria

Considering separately pH-only (acidic) criteria from impedance criteria, by means of the EAET the diagnosis of NERD was confirmed in only 118 of 221 patients (53%) (pH-positive cases). Adding cases with SAP/SI positivity for acid refluxes (47 cases) to the 118 pH-positive cases, NERD diagnosis was confirmed by pH-only criteria in 165 of 221 patients (75%) as compared with 118 of 221 pH-positive cases (53%) (P ¼ .001). Considering impedance criteria, a positive SAP/SI for weakly acidic refluxes was found in 18 of 103 pH-negative patients (17%). Adding SAP/SI positivity for weakly acidic refluxes to pH-only criteria, GERD diagnosis was confirmed in 183 of 221 patients (83%) vs 165 of 221 patients (75%) (P ¼ .048). Adding cases whose only abnormality was a low PSPW index and/or a low MNBI, diagnosis was confirmed in 216 of 221 cases vs 183 of 221 cases (P ¼ .001). Overall, in 221 patients the diagnosis of NERD was confirmed in 75% of cases by pHonly criteria and in 98% of cases by impedance-pH criteria (P ¼ .001).

DISCUSSION

In the present study, we blindly reviewed impedance-pH tracings from 289 patients with clinically proven GERD; indeed, they all complained of the cardinal GERD symptom, ie, recurring heartburn, troublesome enough to require medical consultation and repeatedly abolished by 4-week PPI courses (PPI-dependent heartburn). Two novel impedance parameters, namely the PSPW index and the MNBI, were assessed and resulted significantly lower in ERD than in NERD and in both as compared with 50 healthy controls, confirming their pathophysiologic soundness.8,9 By means of ROC analysis, threshold values for abnormal PSPW index (<61%) and abnormal MNBI (<2292 ohms) were defined. Adopting such cutoff values, the sensitivity of PSPW index and of MNBI was higher in comparison with conventional impedance-pH parameters, namely percentage EAET, number of total refluxes, and percentage bolus exposure in the various GERD subgroups.

The vast majority of patients with heartburn are included in the NERD phenotype because visible mucosal lesions are not found at endoscopy.15 Because a gold standard for GERD diagnosis is lacking,16 recurrent heartburn repeatedly responsive to PPI therapy (PPI-dependent heartburn) can be considered as the clinical diagnostic gold standard.1,2 Only patients with PPI-dependent heartburn were included in our series because patients with extraesophageal syndromes, chest pain, and even regurgitation often do not respond to PPI therapy.2

Impedance-pH monitoring is most often used to diagnose NERD in endoscopy-negative patients with reflux symptoms partially or totally unresponsive to PPI therapy and in PPI-responsive patients before antireflux surgical or endoscopic interventions.1,2 Studies have shown that some patients have a positive symptom-reflux association to weakly acidic refluxes that cannot be detected by pH-only monitoring but can damage esophageal mucosa.15 Unfortunately, symptoms may not occur during 24-hour reflux monitoring. Moreover, accuracy of patients in symptom recording is often far from perfect. As a consequence, SAP/SI may be negative even in several ERD patients, as we found in this series. Therefore, in pH-negative patients a positive SAP/SI indicates reflux-related heartburn,15,16 but a negative SAP/SI does not exclude GERD; indeed, patients with heartburn may respond to PPI therapy despite normal conventional impedance-pH findings.9 More in depth evaluation of impedance-pH tracings could assist in distinguishing reflux-related from reflux-unrelated heartburn. In fact, the PSPW index is lower in patients with GERD than in patients with functional heartburn at on-PPI impedance-pH monitoring.8 In a very recent study, patients with normal conventional impedance-pH parameters who responded to PPI therapy and patients with PPI-responsive hypersensitive esophagus had similar MNBI values, significantly lower than those found in patients with PPI-refractory heartburn.17 Then, in doubtful cases both parameters could assist in GERD diagnosis.

In the present study, by ROC analysis we have defined the cutoff values for PSPW index and MNBI that best separate GERD patients from healthy controls with very high diagnostic accuracy. We confirm that MNBI is directly related to PSPW index,9,17 suggesting that impaired mucosal integrity is a consequence of impaired chemical clearance. According to ROC analysis, the AUC of the PSPW index was significantly greater than that of the other impedance-pH parameters. The AUC of the MNBI could have been negatively affected by the PPI washout period adopted. The time required for impairment of mucosal integrity to recur after PPI withdrawal has not been established and delaying impedance-pH monitoring until heartburn recurs could be more suitable than adopting a standardized 2-week washout period.

In our series, only 118 of 221 patients (53%) with PPI-dependent, endoscopy-negative heartburn were pH-positive, confirming the diagnostic limits of EAET and pH-only monitoring in NERD.9,17 In pH-negative NERD patients, both in SAP/SI positive and in SAP/SI negative cases the PSPW index and the MNBI showed higher sensitivity and overall accuracy than the number of total refluxes and the percentage bolus exposure. Remarkably, PSPW index and MNBI were the only abnormal impedance parameters in pH-negative, SAP/SI negative patients. At least 1 of the 2 was abnormal in 87% of cases, but concordance was only moderate, suggesting that both parameters should be used. NERD was confirmed by pH-only criteria, ie, higher than normal EAET and/or SAP/SI positivity for acid refluxes in 75% of 221 cases. A slight diagnostic gain was observed after adding SAP/SI positivity for weakly acidic refluxes. Notably, when abnormal PSPW index and/or MNBI were also taken into account, NERD diagnosis could be confirmed in the vast majority of cases (98%) by impedance-pH criteria, with a significant diagnostic gain over pH-only criteria.

Calculation of PSPW index and MNBI can easily be carried out during visual analysis of tracings, requiring few minutes only.8,9,17 In this study, we have shown a significant and very high reproducibility for both parameters. Moreover, their applicability is wide; they could be calculated in all 339 tracings included in this multicenter case-series. Because of the high diagnostic accuracy of PSPW index and MNBI, we believe that in patients with normal conventional impedance-pH parameters and negative SAP/SI but abnormal values for these novel impedance parameters, GERD diagnosis cannot be dismissed.

Whether PSPW index and MNBI can prove useful to predict response to surgical or endoscopic antireflux interventions in PPI-responsive and in PPI-refractory GERD remain open issues to be addressed by future outcome studies.

In conclusion, PSPW index and MNBI improve the diagnostic yield of impedance-pH monitoring in GERD. Adding impedance criteria, including calculation of PSPW index and MNBI, to pH-only criteria improves significantly our ability to diagnose GERD.

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TABLE PAGES

Table 1: Baseline Characteristics of Patients With ERD and NERD and of Healthy Controls

	ERD (n = 68)	NERD (n = 221)	HC (n = 50)
Male gender (n) (%)	40/68 (59)	92/221 (42)	23/50 (46)
	$P > .05$ for all pairwise comparisons		
Age (*y*) (mean) (SD)	50 (14)	50 (14)	44 (17)
	$P < .05$ for HC as compared with ERD and NERD		
BMI (*kg*) (mean) (SD)	27 (4)	25 (4)	23 (3)
	$P < .05$ for all pairwise comparisons		
Hiatal hernia (n) (%)	56/68 (85)	108/221(49)	3/50 (6)
	$P < .05$ for all pairwise comparisons		
EAET (%) (mean) (SD)	8.3 (5.5)	5.0 (4.8)	1.0 (1.0)
	$P < .05$ for all pairwise comparisons		
Total refluxes (n) (mean) (SD)	70 (32)	54 (33)	23 (14)
	$P < .05$ for all pairwise comparisons		
Bolus exposure (%) (mean) (SD)	3.0 (2.5)	2.2 (2.5)	0.7 (0.7)
	$P < .05$ for HC as compared with ERD and NERD		
PSPW index (%) (mean) (SD)	20 (9)	40 (16)	80 (13)
	$P < .05$ for all pairwise comparisons		
MNBI (*ohms*) (mean) (SD)	1129 (654)	1789 (812)	2936 (772)
	$P < .05$ for all pairwise comparisons		

BMI, body mass index; HC, healthy controls; SD, standard deviation.

Table 2: Diagnostic Accuracy of Impedance-pH Parameters in Patients With ERD and NERD

	EAET (%)	Total refluxes (%)	Bolus exposure (%)	PSPW index (%)	MNBI (%)
	ERD (n = 68)				
Sensitivity	85	75	59	100	91
Specificity	94	96	96	92	86
PPV	95	96	95	94	90
NPV	82	74	63	100	88
Overall accuracy	89	84	75	97	89
	NERD (n = 221)				
Sensitivity	53	45	36	89	72
Specificity	94	96	96	92	86
PPV	98	98	98	98	96
NPV	31	28	25	65	41
Overall accuracy	61	54	47	89	75

NPV, negative predictive value; PPV, positive predictive value.

Table 3: Diagnostic Accuracy of Impedance Parameters in pH-positive and pH-negative NERD

	Total refluxes (%)	Bolus exposure (%)	PSPW index (%)	MNBI (%)
	pH-positive NERD (n = 118)			
Sensitivity	70	62	99	86
Specificity	96	96	92	86
PPV	98	97	97	94
NPV	58	52	98	73
Overall accuracy	78	73	97	86
	pH-negative NERD (n = 103)			
Sensitivity	16	4	77	56
Specificity	96	96	92	86
PPV	89	67	95	89
NPV	36	33	66	49
Overall accuracy	42	34	82	66

NPV, negative predictive value; PPV, positive predictive value.

Table 4: Diagnostic Accuracy of Impedance Parameters in pH-negative, SAP/SI Positive, and SAP/SI Negative NERD

	Total refluxes (%)	Bolus exposure (%)	PSPW index (%)	MNBI (%)
pH-negative, SAP/SI positive NERD (n = 65)				
Sensitivity	25	6	82	52
Specificity	96	96	92	86
PPV	89	67	93	83
NPV	49	44	79	58
Overall accuracy	56	45	86	67
pH-negative, SAP/SI negative NERD (n = 38)				
Sensitivity	0	0	68	63
Specificity	96	96	92	86
PPV	0	0	87	77
NPV	56	56	79	75
Overall accuracy	55	55	82	76

NPV, negative predictive value; PPV, positive predictive value.

FIGURE PAGES

Figure 1: PSPW. Impedance-pH tracing showing antegrade 50% drop in impedance relative to pre-swallow baseline originating in most proximal impedance site, reaching all distal impedance sites, and followed by at least 50% return to baseline in distal impedance sites (bolus exit) (arrow). BCT, bolus clearance time; LES, lower esophageal sphincter; MII, multichannel intraluminal impedance.

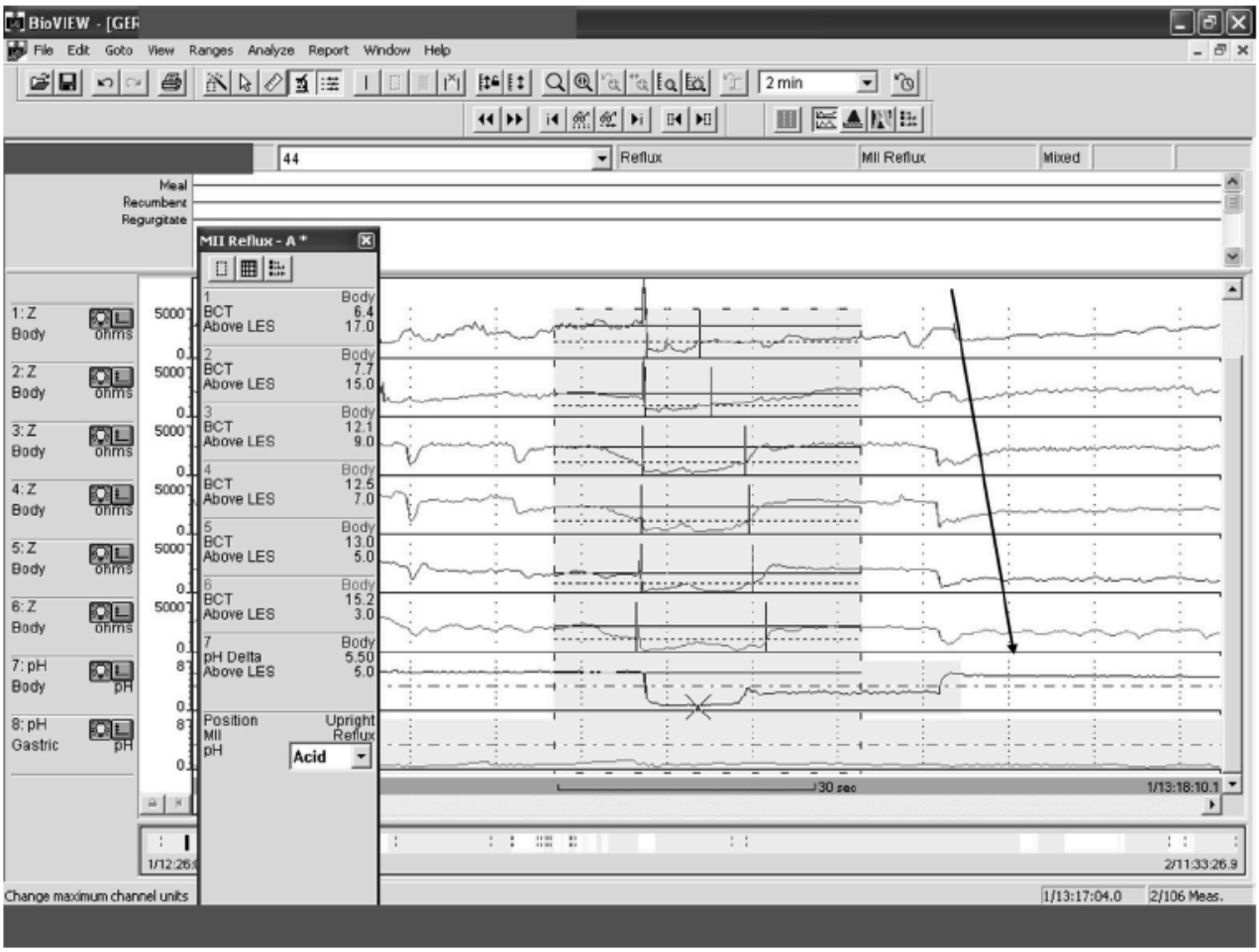

Figure 2: ROC curves. AUC of PSPW index (0.977) (black curve) was significantly greater than that of other impedance-pH parameters (gray curves) ($P < .001$). Best cutoff values for PSPW index and MNBI were 61% and 2292 ohms, respectively. Best cutoff values for EAET, number of total refluxes, and bolus exposure were 3.2%, 48, and 1.9%, respectively.