TITLE: Association Between Baseline Impedance Values and Response Proton Pump Inhibitors in Patients with Heartburn

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CONFLICTS OF INTEREST

The authors disclose no conflicts

Abbreviations used in this paper:

AET, acid exposure time; **FH**, functional heartburn; **GERD**, gastroesophageal reflux disease; **GIS**, Gastroesophageal Reflux Disease Impact Scale; **HE**, hypersensitive esophagus; **MII-pH**, multichannel intraluminal impedance and pH monitoring; **NERD**, nonerosive reflux disease; **PPI**, proton pump inhibitor; **PSPW**, post-reflux swallow-induced peristaltic wave; **SAP**, symptom association probability; **SI**, symptom index; **VAS**, visual analogue scale.

ABSTRACT

BACKGROUND & AIMS: Esophageal impedance measurements have been proposed to indicate the status of the esophageal mucosa and might be used to study the roles of the impaired mucosal integrity and increased acid sensitivity in patients with heartburn. We compared baseline impedance levels among patients with heartburn who did and did not respond to proton pump inhibitor (PPI) therapy, along with the pathophysiological characteristics of functional heartburn (FH).

METHODS: In a case-control study, we collected data from January to December 2013 on patients with heartburn and normal findings from endoscopy who were not receiving PPI therapy and underwent impedance pH testing at hospitals in Italy. Patients with negative test results were placed on an 8-week course of PPI therapy (84 patients received esomeprazole and 36 patients received pantoprazole). Patients with more than 50% symptom improvement were classified as FH/PPI responders and patients with less than 50% symptom improvement were classified as FH/PPI non-responders. Patients with hypersensitive esophagus and healthy volunteers served as controls. In all patients and controls, we measured acid exposure time, number of reflux events, baseline impedance, and swallow-induced peristaltic wave indices.

RESULTS: FH/PPI responders had higher acid exposure times, numbers of reflux events, and acid refluxes compared with FH/PPI non-responders ($P < .05$). Patients with hypersensitive esophagus had mean acid exposure times and numbers of reflux events similar to those of FH/PPI responders. Baseline impedance levels were lower in FH/PPI responders and patients with hypersensitive esophagus, compared with FH/PPI nonresponders and healthy volunteers ($P < .001$). Swallow-induced peristaltic wave indices were similar between FH/PPI responders and patients with hypersensitive esophagus.

CONCLUSIONS: Patients with FH who respond to PPI therapy have impedance pH features similar to those of patients with hypersensitive esophagus. Baseline impedance measurements might allow for identification of patients who respond to PPIs but would be classified as having FH based on conventional impedance-pH measurements.

Keywords: GERD; pH Monitoring; Functional GI Disorder; pH-Impedance Monitoring.

INTRODUCTION

Nonerosive reflux disease (NERD) patients are markedly heterogeneous from both a pathophysiological and clinical point of view, and should be characterized appropriately by means of 24-hour esophageal multichannel intraluminal impedance and pH monitoring (MII-pH).[1] Indeed, the advent of MII-pH has enabled the identification of acid, weakly acidic, and weakly alkaline refluxes with a consequent added value in differentiating patients with hypersensitive esophagus (HE) (i.e., negative endoscopy, physiological acid exposure time, AET, and positive symptom-reflux association) from patients with functional heartburn (FH) (i.e., negative endoscopy, physiological AET, negative symptom/reflux association, and a negative response to acid suppression therapy).[2–4] On the other hand, recent studies highlighted some MII-pH limitations, such as the day-to-day variability or the drawbacks of the current reflux-symptom association indexes.[5,6] In addition, the response to proton pump inhibitors (PPIs) has limited the ability to identify gastroesophageal reflux disease (GERD) patients.[7–9]

Recently, it was suggested that low esophageal basal impedance measurements may reflect the status of the esophageal mucosa and thus may be used to study the role of the impaired mucosal integrity and increased acid sensitivity in patients with heartburn.[10–12] According to previous findings, baseline impedance levels may be useful to increase the diagnostic sensitivity of MII-pH monitoring.[13,14] Based on this evidence, the aim of the present study was to compare baseline impedance levels in patients with heartburn and pathophysiological characteristics related to FH divided into 2 groups on the basis of symptom relief after PPIs. Moreover, we compared these results with a group of patients with HE and healthy volunteers (HVs). Considering that impairment of chemical clearance is a primary pathophysiological mechanism specific to GERD,[15] our study secondly aimed to evaluate the efficacy of esophageal chemical clearance in the same 3 subgroups of patients, to correlate it with baseline impedance levels.

MATERIALS AND METHODS

Throughout 2013, we prospectively enrolled a group of consecutive endoscopy-negative patients, with heartburn (with/without regurgitation), presenting to the outpatient motility laboratory at the Universities of Genoa, Pisa, Padua, and the Hospital of Modena (Italy).

The presence of erosive esophagitis and other abnormalities was excluded by upper endoscopy, performed in each earlier-listed Divisions of Gastroenterology within 6 months before the visit. Each patient discontinued PPIs or H2-receptor antagonists at least 20 days before undergoing endoscopy.

After the first visit, a single dose of esomeprazole or pantoprazole 40 mg was prescribed to each patient for 8 weeks.

Eighty-four patients were treated with esomeprazole and 36 patients were treated with pantoprazole. Symptoms were evaluated both before and after therapy through a validated questionnaire (GERD Impact Scale [GIS]) and a visual analogue scale (VAS) for heartburn as previously described.[8] Then, all subjects underwent stationary esophageal manometry and 24-hour MII-pH off-therapy (14-day wash-out). Patients were allowed to take only alginates, on an as-needed basis, as rescue therapy for controlling heartburn.[16] The methodology of probe calibration, catheter placement, patient instruction, and performance was described previously.[1] A group of 20 HVs, who never experienced GERD symptoms and/or took PPIs, underwent esophageal manometry and MII-pH off-therapy.

Multichannel Intraluminal Impedance and pH Monitoring Data Analysis

At the end of the recording period, MII-pH tracings were reviewed manually by 3 investigators (N.d.B., E.S., and M.F.) to ensure accurate detection and classification of reflux episodes and baseline impedance values. MII-pH data were used to determine the number and type of reflux episodes as well as AET in each patient. In particular, distal esophageal AET was defined as the total time with a pH if less than 4, divided by the total monitoring time. A total (24-h) percentage time the pH was less than 4 for less than 4.2% of the time was considered normal.[1,17] Acid, weakly acidic, and weakly alkaline refluxes were defined according to the previously published studies.[18] The proximal reflux extent was defined as a decrease in impedance recorded 15 cm
from the lower esophageal sphincter. Finally, the correlation between symptoms and reflux events with the Symptom Index (SI) and the symptom association probability (SAP) was evaluated for each patient as previously described.[14]

Baseline impedance levels were assessed from the most distal channel (z1, 3 cm above the lower esophageal sphincter) during the overnight rest, at 3 time points, as previously described.[14] Moreover, for each patient, we assessed the chemical clearance according to the postreflux swallow-induced peristaltic wave (PSPW) index.[15]

The PSPW is defined as the number of refluxes followed within 30 seconds by a swallowing-induced peristaltic wave, divided by the number of total refluxes. The Rome III criteria defined FH as the occurrence of chronic retrosternal burning in the absence of a GERD diagnosis (ie, negative endoscopy and pH monitoring) and the lack of response to acid-suppressive treatment.[4] According to endoscopy and MII-pH data, patients were included in the study in case of normal endoscopy, normal AET, and normal number of reflux episodes.

Within this group, we enrolled both patients with a positive association between symptoms and refluxes based on a positive SI (if > 50%) and a positive SAP (if > 95%) as previously described,[19] considered as affected by HE, and patients with a lack of association between symptoms and refluxe, thus suspected of having FH. Within the latter, we evaluated symptom relief after PPI therapy using GIS and VAS scores. Then, we stratified these patients into 2 groups by means of therapeutic outcome as follows: FH/PPI-responder, which consisted of 40 patients who reported satisfactory symptom relief for heartburn (>50% compared with baseline values); and FH/PPI-non-responder, which consisted of an equivalent number of patients, matched for sex, who reported unsatisfactory symptom relief for heartburn (<50% compared with baseline values). Finally, MII-pH parameters, including AET, number of refluxes, baseline impedance values, and PSPW index were collected from HVs and compared with those collected from FH/PPI-responder, FH/PPI-non-responder, and HE.

Statistical Analysis

Data are expressed as means and SD. Statistical tests to compare groups of subjects included the Student t test and analysis of variance for difference in mean values, the Mann–Whitney U test and the Kruskal–Wallis test for skewed variables, and the Pearson chi-squared test (with Yates continuity correction as appropriate) for differences in counts and frequency. Post hoc comparisons were performed using the Bonferroni correction in case of a significant analysis of variance result. The Kolmogorov–Smirnov test was used to assess the normality of data. Pearson analysis was performed to find a correlation between baseline impedance values and the PSPW index. A receiver operator characteristic analysis was performed to detect a baseline impedance cut-off value. A P value less than .05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 120 patients were included in the study and divided further into 3 distinct groups matched for sex. The prevalence of a hiatal hernia did not differ between HE, FH/PPI-responders, and FH/PPI-non-responders (P= 0.184). Detailed results are reported in **Table 1**.

As to the symptom relief after PPI therapy, the mean value of the GIS decreased from 1.83 before therapy to 0.33 after therapy within the HE group (P < 0.001), and similarly decreased from 1.79 before therapy to 0.29 after therapy in the FH/PPI-responders (P < 0.001). By contrast, within FH, the GIS score remained unmodified before and after therapy, ranging from 1.78 to 1.53.

Moreover, the VAS questionnaire, indicating heartburn perception, changed from 93.4 before therapy to 18.9 after therapy in HE (P < .001), and from 90.4 to 21.2 in FH/PPI-responders (P < .001). No significant modifications were found in FH/PPI-non-responders, in whom heartburn perception changed from 92.7 to 68.9.

Pathophysiological Investigations

Combined MII-pH was well tolerated by all subjects and no technical failures occurred. The results yielded by MII-pH testing are shown in **Table 2**. The median number of heartburn episodes reported during the 24-hour MII-pH test was 4 (25th–75th interquartile range, 2.75–5) in HE, 4 (25th–75th interquartile range, 3–5) in FH/PPI responders, and 3 (25th–75th interquartile range, 2–4) in FH. No symptoms were recorded from HVs.

No differences were observed between HE and FH/PPI-responders in pathophysiological MII-pH parameters. Of note, FH/PPI-responders showed an increase of MII-pH parameters when compared with FH/PPI non-responders (P < 0.001) and HVs (P < 0.001). No differences were recorded between FH/PPI-non-responders and HVs.

Baseline impedance levels in HE were similar (at 1 am, 1834.7±585.9; at 2 am, 1950.4±504.9; and at 3 am, 1734±468.6) to those recorded in FH/PPI-responders (at 1 am, 2071.5±674.2; at 2 am, 2153.6±690; and at 3 am, 2196.8±690.6; P= 0.338), and lower as compared with those recorded in FH (at 1 am, 3719±1098.9; at 2 am, 3846.9±909.7; and at 3 am, 3872.7±796.7; P < 0.001), and in HVs (at 1 am, 3317.7±953; at 2 am, 3443.4±950.1; and at 3 am, 3522.6±915.6) at all 3 time points (P< 0.001). No differences were found between FH/PPI non-responders and HVs (P= 0.096) (**Figure 1**). The PSPW index in HE was similar to the one in FH/PPI-responders, although it was lower than the one in FH/PPI non-responders (P < 0.001) and in HVs (P < 0.001). No differences were observed between FH/PPI-non-responders and HVs (P= 0.4810). The baseline impedance cut-off value for

PPI-responder patients obtained with a receiver operator characteristic analysis was 2446 Ohms (sensitivity, 97.5%; specificity, 78.6%; positive predictive value, 82.2%; and negative predictive value, 96.3%). Baseline impedance values showed a good inverse correlation with AET ($r= -0.547$; $P < 0.001$), and with the total number of reflux events ($r= -0.673$; $P < 0.001$). We found a strong correlation between the mean baseline impedance levels and the PSPW index (**Figure 2**).

DISCUSSION

Our study specifically tested the hypothesis that novel pathophysiological parameters, such as impedance baseline values, which indicate the presence of an impaired mucosal integrity, could improve the diagnostic accuracy of MII-pH and, thus, improve the possibility of clearly distinguishing between patients with HE and patients with FH.[20] Accordingly, we found the following 3 results. First, FH/PPI-responders had similar AET, total reflux number, acid reflux number, proximal reflux number, as well as similar baseline impedance values and PSPW index to HE. Second, FH/PPI-responders had higher AET, total reflux number, acid reflux number, proximal reflux number, and, at the same time, lower baseline impedance levels and a PSPW index as compared with FH/PPI-nonresponders. Third, FH/PPI-non-responders showed similar baseline impedance values and PSPW indexes to HVs. Therefore, this study found that esophageal baseline impedance measurements might allow identification of reflux patients who are not confirmed by MII-pH monitoring, likely owing to the day-to-day variability or the limitations of the current reflux-symptom association indexes. Our data show that baseline impedance values are a promising MII-pH parameter to increase the sensitivity of MII-pH tests in diagnosing GERD, particularly in patients with physiological AET. Moreover, these data suggest that excluding patients from endoscopic and/or surgical treatments for GERD based on a negative pH(-impedance) test may be incorrect and further testing should be recommended. It is well known that NERD is an umbrella term that includes patients who are markedly heterogeneous from a pathophysiological and clinical point of view.[21] In addition, the mechanisms responsible for reflux perception are not yet fully understood. Although the mechanisms of acid injury in the esophageal epithelium have been investigated thoroughly,[22] other gastric/duodenal components (ie, pepsin, bile acids) and endogenous factors (ie, psychological stress) can be involved as a cause of impaired mucosal integrity.[23] Moreover, there is often a high discrepancy between esophageal exposure to acid and the severity of reported reflux symptoms.[24] This has led to the belief that visceral hypersensitivity plays a relevant role in the pathophysiology of GERD, although with variance between subtypes of GERD.[25] As to NERD patients, Woodland et

al. [12] suggested that increased acid perception was associated with a “vulnerable” mucosal integrity maintained by repetitive acid exposure with slow mucosal recovery. In this context, some researchers have hypothesized that the presence of microscopic damage (ie, dilated intercellular spaces) increases esophageal permeability to acid and, theoretically, should be responsible for symptom generation in NERD.[10,26,27] However, it has been reported that the presence of dilated intercellular spaces did not always correlate with the presence of impaired mucosal integrity.[28]

Our study specifically assessed impaired mucosal integrity, by means of baseline impedance levels, in HE patients compared with FH and PPI responder patients with negative MII-pH, FH/PPI-responders. We have shown that FH/PPI-responder patients have similar AET, number of acid refluxes, and baseline impedance levels to HE patients. Furthermore, FH/PPI-responder patients have a significantly higher AET and acid reflux number, and lower baseline impedance levels as compared with FH/PPI-non-responder patients. In keeping with a spectrum model of GERD in which pathophysiological abnormalities increase in parallel with the severity of the disease,[29] it is reasonable to hypothesize that baseline impedance levels increase in parallel with the severity of GERD, from healthy and FH subjects to HE, NERD, and erosive reflux disease.

We assessed baseline impedance levels at night because there is a greater facility to avoid both swallows, which likely is attributable to the inhibition of the swallowing reflex,[30] and refluxes, which usually occur in small number during the night. Moreover, no diurnal variations in baseline impedance levels have been observed in GERD patients during the 24-hour measurement.[11] Considering previous data highlighting the absence of significant differences in proximal esophageal baseline impedance levels between GERD patients and healthy controls,[10,11,31] we calculated baseline impedance levels in the distal esophagus only. In addition, we performed 10-minute measurement baseline levels because short time measurements of baseline impedance values are reliably representative of long period measurements.[14]

Recently, Frazzoni et al. [15] found that impairment of esophageal chemical clearance, as represented by the PSPW index, represents a primary pathophysiological mechanism specific to GERD because it is unaffected by medical or surgical therapy. After a reflux episode, esophageal clearance depends on volume and chemical clearance. Volume clearance consists of a secondary peristaltic wave, caused by a local reflex, which removes the highest percentage of the refluxate from the esophagus.

However, neutralization of the distal esophageal lumen occurs only after transport of saliva by a swallow-induced peristaltic wave. The efficiency of esophageal chemical clearance mechanisms can be assessed in the clinical setting by MII-pH, which allows assessment of swallow-induced peristaltic waves after reflux episodes (ie, PSPW index). Of note, impairment of esophageal chemical clearance

appears to have a major role in the development and persistence of esophageal mucosal damage in GERD and a high diagnostic accuracy in distinguishing GERD from non-GERD subjects. Indeed, the PSPW index was significantly more pronounced in patients with erosive reflux disease than in patients with NERD. On the other hand, impairment of chemical clearance was not found in FH and HVs.[15] In the present study, we observed that HE patients had a PSPW value lower than FH and HVs. In addition, FH/PPI-responder patients showed PSPW values very close to HE, and significantly different from FH/PPI-non-responders and HVs. In addition, a recent study by our group showed that there was a direct relationship between baseline impedance levels and the PSPW index.[14]

Our study pointed out that a subgroup of patients with GERD symptoms did not show any association between symptoms and refluxes despite their good response to PPI therapy (FH/PPI-responder). This group recorded similar 24-hour MII-pH parameters to those who were FH/PPI-non-responders, including the lack of association between symptoms and refluxes based on SI and SAP analysis. Although these indexes are used commonly in clinical practice, there is uncertainty about their validity to determine a reliable correlation between symptoms and refluxes in GERD patients.[6] Indeed, the SI and SAP have never obtained a formal validation. The SI has been considered a non-suitable index to create a causal relationship between reflux and symptoms.[32] In a prospective study, the SAP has shown a high discordance rate (32%) with the results of a PPI trial.[33] In our opinion, the SI and SAP are workable and useful in clinical practice and they have to be calculated during 24-hour MII-pH examinations to clearly separate the subsets of patients with real GERD from the subgroup with FH, which does not pertain to GERD. However, we note that they have some limitations and up and coming parameters, such as PSPW and baseline impedance levels, which might be useful to improve the diagnostic ability of MII-pH, thus permitting more precise subgrouping of patients with NERD and distinction of FH from reflux disease.

Among the limitations of our study, we would like to point out that there were a great number of patients responding to PPIs in the HE and FH groups. However, because this investigation was designed primarily as a pathophysiological study, no placebo-controlled treatment was included. Thus, we cannot exclude a relevant placebo effect in our patients.

In conclusion, this study evaluated up and coming variables of MII-pH study (baseline impedance levels and the PSPW index) in patients with heartburn and negative MII-pH, but positive response to PPIs, to assess the differences and similarities with both FH/PPI non-responders and HE patients. Based on our data, in FH/PPI-responder patients, baseline impedance levels, as well as the PSPW index and MII-pH features, are strongly close to the measurements recorded in HE patients. The only difference observed between FH/PPI-responders and HE was related to the symptom reflux analysis.

Moreover, considering the presence of lower baseline impedance levels in FH/PPI-responders and HE than in FH/PPI-non-responders and HVs, we believe that the assessment of esophageal baseline impedance values could represent a marker for reflux-induced changes of the esophageal mucosa and could help to identify patients affected by HE, especially when reflux-symptom association analysis fails to do so. Of note, HE patients are considered to have GERD and they have similar benefits from anti-reflux surgery as patients with pathologic degrees of acid exposure.[34] In this context, the baseline impedance value and the PSPW index could be helpful in clinical practice to classify patients correctly who would respond to medical and/or surgical treatments similar to patients with HE. However, the results from this study warrant further validation by prospective outcome studies.

REFERENCES

1. Savarino E, Zentilin P, Tutuian R, et al. The role of nonacid reflux in NERD: lessons learned from impedance-pH monitoring in 150 patients off therapy. Am J Gastroenterol 2008;103:2685–2693.
2. Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. Dig Liver Dis 2011;43:542–547.
3. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024–1031.
4. Galmiche JP, Clouse RE, Balint A, et al. Functional esophageal disorders. Gastroenterology 2006;130:1459–1465.
5. Hershcovici T, Wendel CS, Fass R. Symptom indexes in refractory gastroesophageal reflux disease: overrated or misunderstood? Clin Gastroenterol Hepatol 2011;9:816–817.
6. 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;9:868–874.
7. Bytzer P, Jones R, Vakil N, et al. Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2012;10:1360–1366.
8. de Bortoli N, Martinucci I, Savarino E, et al. Proton pump inhibitor responders who are not confirmed as GERD patients with impedance and pH monitoring: who are they? Neurogastroenterol Motil 2014;26:28–35.
9. Numans ME, Lau J, de Wit NJ, et al. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med 2004;140:518–527.
10. Farre R, Blondeau K, Clement D, et al. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. Gut 2011;60:885–892.
11. Kessing BF, Bredenoord AJ, Weijenborg PW, et al. Esophageal acid exposure decreases intraluminal baseline impedance levels. Am J Gastroenterol 2011;106:2093–2097.
12. Woodland P, Al-Zinaty M, Yazaki E, et al. In vivo evaluation of acid-induced changes in oesophageal mucosa integrity and sensitivity in non-erosive reflux disease. Gut 2013;62:1256–1261.

13. Ribolsi M, Emerenziani S, Borrelli O, et al. Impedance baseline and reflux perception in responder and non-responder nonerosive reflux disease patients. Scand J Gastroenterol 2012;47:1266–1273.
14. Martinucci I, de Bortoli N, Savarino E, et al. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. Neurogastroenterol Motil 2014;26:546–555.
15. Frazzoni M, Manta R, Mirante VG, et al. Esophageal chemical clearance is impaired in gastro-esophageal reflux disease–a 24-h impedance-pH monitoring assessment. Neurogastroenterol Motil 2013;25:399–406, e295.
16. Savarino E, de Bortoli N, Zentilin P, et al. Alginate controls heartburn in patients with erosive and nonerosive reflux disease. World J Gastroenterol 2012;18:4371–4378.
17. Zentilin P, Iiritano E, Dulbecco P, et al. Normal values of 24-h ambulatory intraluminal impedance combined with pH-metry in subjects eating a Mediterranean diet. Dig Liver Dis 2006;38:226–232.
18. Sifrim D. Acid, weakly acidic and non-acid gastro-oesophageal reflux: differences, prevalence and clinical relevance. Eur J Gastroenterol Hepatol 2004;16:823–830.
19. Savarino E, Tutuian R, Zentilin P, et al. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. Am J Gastroenterol 2010;105:1053–1061.
20. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. J Gastroenterol 2012;47:159–168
21. Savarino E, Zentilin P, Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nat Rev Gastroenterol Hepatol 2013;10:371–380.
22. Orlando RC. The integrity of the esophageal mucosa. Balance between offensive and defensive mechanisms. Best Pract Res Clin Gastroenterol 2010;24:873–882.
23. Farre R. Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? Neurogastroenterol Motil 2013;25:783–799.
24. Bredenoord AJ, Weusten BL, Timmer R, et al. Characteristics of gastroesophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. Am J Gastroenterol 2006;101:2470–2475.
25. Knowles CH, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. Gut 2008;57:674–683.
26. Dent J. Microscopic esophageal mucosal injury in nonerosive reflux disease. Clin Gastroenterol Hepatol 2007;5:4–16.

27. Savarino E, Zentilin P, Mastracci L, et al. Microscopic esophagitis distinguishes patients with non-erosive reflux disease from those with functional heartburn. J Gastroenterol 2013;48:473–482.
28. Farre R, van Malenstein H, De Vos R, et al. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. Gut 2008;57:1366–1374.
29. Savarino E, Zentilin P, Frazzoni M, et al. Characteristics of gastro-esophageal reflux episodes in Barrett's esophagus, erosive esophagitis and healthy volunteers. Neurogastroenterol Motil 2010;22:1061–e280.
30. Orr WC, Johnson LF, Robinson MG. Effect of sleep on swallowing, esophageal peristalsis, and acid clearance. Gastroenterology 1984;86:814–819.
31. Ribolsi M, Cicala M. Baseline impedance levels and structural and functional integrity of the esophageal mucosa: is acid still the only player? Am J Gastroenterol 2012;107:1104; author reply 1105.
32. Clark WC, Clark SB. Application of the medical decision-making model to esophageal reflux disease: commentary on a study by Breumelhof and Smout. Am J Gastroenterol 1992;87:924–926.
33. Taghavi SA, Ghasedi M, Saberi-Firoozi M, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. Gut 2005;54:1067–1071.
34. Broeders JA, Draaisma WA, Bredenoord AJ, et al. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication. Br J Surg 2009;96:1023–1030.

TABLE PAGE

Table 1. Epidemiologic Characteristics of Patients With HE, FH/PPI-Responders, FH/PPI-Nonresponders, and HVs.

	HE (40 patients)	FH/PPI-responders (40 patients)	FH/PPI-nonresponders (40 patients)	HVs	*P* (all groups)
Male/female	10/30	10/30	10/30	10/10	NS
Mean age (±SD), *y*	54.6 ± 14	52.8 ± 10.6	53.7 ± 10.4	49.9 ± 14.7	.847
BMI	23.3 ± 3.1	23.9 ± 3.6	24.3 ± 3.8	24.1 ± 3.5	.947
Smokers	7 (17.5%)	6 (15%)	7 (17.5%)	3 (15%)	.983
Alcohol, 2–3 U/d	4 (10%)	5 (12.5%)	4 (10%)	2 (10%)	.979
Coffee, 2 cups/d	13 (32.5%)	14 (35%)	12 (30%)	5 (25%)	.877
Hiatal hernia	20 (50%)	17 (42.5%)	15 (37.5%)	0	.524

Legend: BMI=body mass index

Table 2. MII-pH Analysis with Baseline Impedance Values and PSPW Index in patients with HE, FH/PPI-responders, FH/PPI-nonresponders, and HVs.

	HE (40 patients)	FH/PPI-responders (40 patients)	FH/PPI-nonresponders (40 patients)	HVs (20 subjects)	*P* (HE vs FH/PPI-responders)
AET	2.3 ± 1.8[a]	1.9 ± 1[b]	0.6 ± 0.6	0.7 ± 0.6	.2229
Tot number of refluxes	34.6 ± 10.4[a]	30.4 ± 9.3[b]	23.5 ± 7.9	17.9 ± 10.8	.0606
Proximal refluxes	10 ± 4.9[a]	11 ± 5.3[b]	7.6 ± 3.8	9.5 ± 9.5	.3836
Acid refluxes	20 ± 7.6[a]	17.1 ± 8[b]	10 ± 6.9	11.7 ± 8.4	.1005
Nonacid refluxes	13 ± 8.8	12.4 ± 8.1	12.8 ± 6.8	12.7 ± 6.2	.7519
SAP	Positive	Negative	Negative	NA	NA
SI	Positive	Negative	Negative	NA	NA
Baseline mean	1839.7 ± 467.6[a]	1949.6 ± 548.8[b]	3812.8 ± 810.2	3463.6 ± 915.6	.3380
PSPW index	55.9 ± 4.6[a]	56.7 ± 8.2[b]	74.3 ± 8.2	76.1 ± 13	.5920

NA, not assessed.
[a] $P < 0.05$ HE vs FH and HVs.
[b] $P < 0.05$ FH/PPI-responders vs HVs and FH/PPI-non-responders.

FIGURE PAGES

Figure 1. Mean baseline impedance levels in all subgroups of patients.

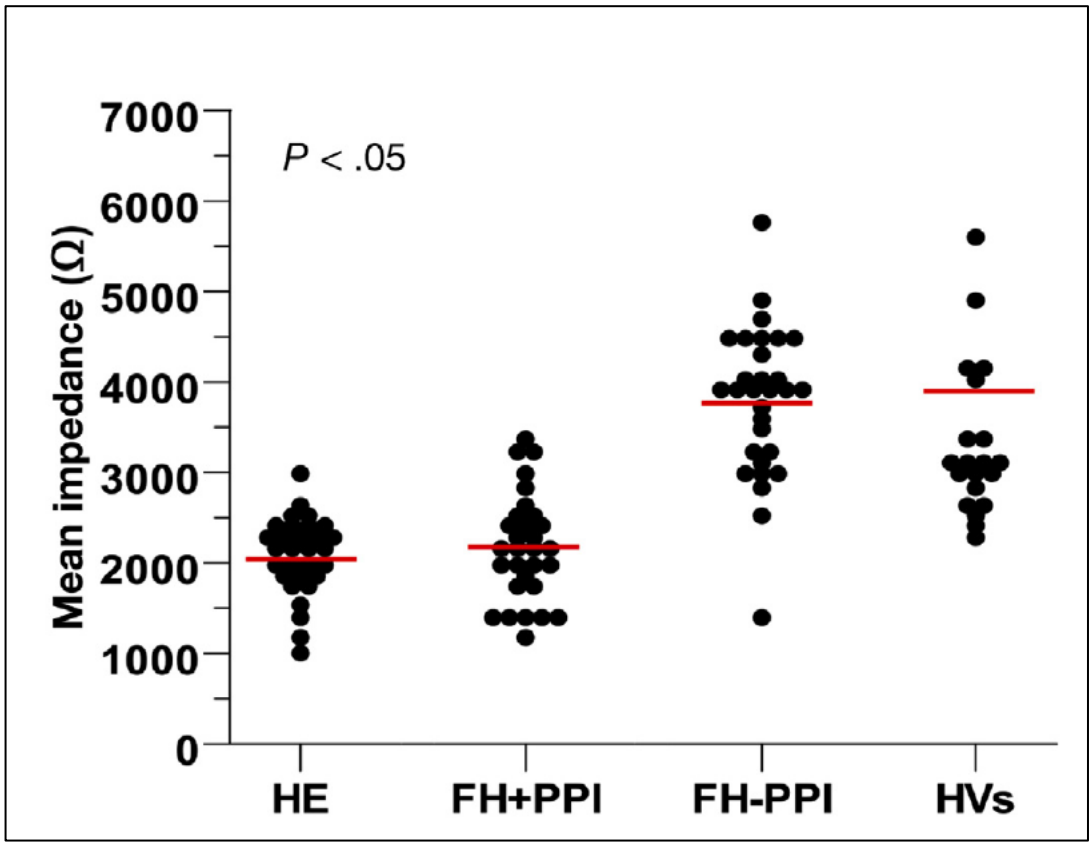

Figure 2. Linear correlation between the PSPW index and baseline impedance levels.