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Tenca, Andrea

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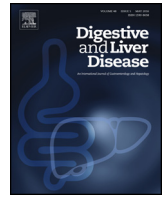
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Alimentary Tract

Esophageal chemical clearance and baseline impedance values in patients with chronic autoimmune atrophic gastritis and gastro-esophageal reflux disease



Andrea Tenca^{a,b,*}, Nicola de Bortoli^c, Aurelio Mauro^a, Marzio Frazzoni^d,
Edoardo Savarino^e, Sara Massironi^a, Salvatore Russo^c, Lorenzo Bertani^c, Santino Marchi^c,
Roberto Penagini^a

^a Gastroenterology and Endoscopy Unit, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

^b Clinic of Gastroenterology, Department of Internal Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

^c Division of Gastroenterology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

^d Digestive Pathophysiology Unit, Baggiovara Hospital, Modena, Italy

^e Division of Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy

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ABSTRACT

Background: The factors influencing new markers of gastro-esophageal reflux disease detected by impedance-pH monitoring – mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave (PSPW) index – need to be evaluated.

Aim: To compare endoscopy-negative heartburn with chronic autoimmune atrophic gastritis (CAAG).

Materials and methods: 24 patients with CAAG, 25 with non-erosive reflux disease (NERD) and 25 with functional heartburn (FH) were included. In all patients the main impedance-pH monitoring parameters were calculated.

Results: CAAG and NERD patients had a number of reflux events (non-acid ones being more common among the former group) which was higher than that found in FH ($p < 0.001$). MNBI decreased progressively in FH (>3000 Ohm), CAAG (>2000 Ohm) and NERD (<1000 Ohm) patients ($p = 0.0046$). The PSPW index was similar between CAAG and NERD patients but significantly lower in comparison to FH ($p < 0.0001$).

Conclusion: Patients with CAAG have evidence of non-acid reflux based on the high number of reflux events and confirmed by low values of MNBI and PSPW index. MNBI is a strong marker of acid/non-acid reflux-induced mucosal damage, whereas the PSPW index can reliably discriminate patients with reflux from those with FH, independently of the acidity of refluxate.

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1. Introduction

Chronic autoimmune atrophic gastritis (CAAG) is a disease characterized by an immune-mediated loss of the parietal cells of the stomach resulting in hypo/achlorhydria [1]. The disease may lead to iron deficiency anemia and pernicious anemia [2]. These patients

are frequently affected by upper gastrointestinal symptoms, such as dyspepsia, bloating or epigastric pain.

Recently Tenca et al. [3] described the prevalence of gastro-esophageal reflux disease (GERD) in patients with CAAG. They observed that acid secretion has markedly decreased and acid reflux events are infrequent and, as a consequence, the PPI response is low. For this reason GERD diagnosis is frequently underestimated.

However, weakly acidic reflux episodes are known to give rise to symptoms, such as heartburn, regurgitation, or cough [4–6]. Still, upper digestive symptoms can be functional in CAAG patients and their development favored, on one side, by the low level of acid secretion (which would render the digestive process more difficult) and, on the other, by anxiety, depression, or somatization [3,7] related to the patient's awareness about the risk of malignancy [8].

* Corresponding author at: Gastroenterology and Endoscopy Unit, Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, University of Milan, Via Francesco Sforza 35, 20122 Milan, Italy. Fax: +39 02 503 20403.

E-mail address: ante14@hotmail.it (A. Tenca).

Esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring is considered as the gold standard for the evaluation of patients with GERD symptoms, since it can characterize the reflux episodes on the basis of their chemical composition (i.e., acid; Ac and non-acid; NA) [9] and it also allows the differentiation between patients affected by functional vs. organic disorder [10].

Recently, two novel impedance parameters evaluating esophageal chemical clearance and mucosal integrity, namely the post-reflux swallow-induced peristaltic wave (PSPW) index [11,12] and the mean nocturnal baseline impedance (MNBI) [13–15] 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 often restored only after voluntary swallowing is elicited by an esophago-salivary reflex mediated through vagal afferents and delivering salivary bicarbonate and epidermal growth factor (chemical clearance) [11]. According to previous findings, both the PSPW index and MNBI may be useful to increase the diagnostic sensitivity of MII-pH monitoring [12].

This study aimed at evaluating: (1) which factors affect MNBI and PSPW (i.e., acid and non-acid reflux) and (2) whether these parameters are useful in discriminating between patients with GERD vs. FH.

2. Material and methods

2.1. Study design

This is a multi-center retrospective observational analysis of MII-pH monitoring data.

2.2. Study protocol

During September 2015, data from three different prospective series [3,12] with specific clinical and MII-pH monitoring patterns were retrospectively reviewed. The three groups respectively comprised: 24 patients with CAAG and evidence of GERD on MII-pH monitoring study (named GERD-CAAG patients); 25 patients with heartburn diagnosed as NERD; and 25 patients with heartburn but no pathophysiological characteristics of GERD (functional heartburn, FH group).

All the subjects had undergone stationary esophageal manometry in order: (1) to determine the position of the lower esophageal sphincter (LES) by using the stationary pull-through technique [16,17] and (2) to exclude the presence of severe abnormalities of peristalsis and/or LES relaxation according to conventional manometry criteria (i.e., achalasia and scleroderma esophagus) [17]. Then, 24 h MII-pH esophageal monitoring off-therapy (i.e. wash-out from PPIs and histamine H₂-receptor antagonists at least 10–14 days before the test) was performed as previously described [3,12]. During the wash-out period only alginates on an as-needed basis were allowed [18].

2.3. Patients

2.3.1. Patients with GERD-CAAG

In all the 24 patients, CAAG was diagnosed on the basis of the following criteria: (i) evidence of mainly body/fundus chronic gastritis with loss of gastric glandular cells and replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue, as evaluated according to the Sydney classification [19] in four samples of gastric mucosa (two taken from the antrum and two from the body of the stomach); (ii) hypergastrinemia and (iii) positive anti-parietal cells or intrinsic factor antibody in a blood sample. Additionally, any *H. pylori* infection was assessed in all the patients

via the same histologic samples and eradicated when positive: its eradication was verified by urea breath test and it was successful in all of them. All the patients underwent a MII-pH monitoring study and the presence of GERD was defined as follows: (1) abnormal acid exposure time (AET) and/or increased number of total refluxes and/or a positive Symptoms Index (SI)/Symptom Association Probability (SAP) (see below “MII-pH monitoring analysis”).

2.3.2. Patients with endoscopy-negative heartburn

The inclusion criteria for endoscopy-negative heartburn patients were: age older than 18 years; complaints of heartburn with/without regurgitation at least three times a week for 6 months in the previous year. The exclusion criteria were: pregnancy (excluded by urine analysis) and/or breast feeding, eating disorders, history of thoracic/esophageal/gastric surgery, underlying psychiatric illness or psychiatric therapies, use of non-steroidal anti-inflammatory drugs and aspirin, peptic ulcer or erosive esophagitis at previous endoscopy. The presence of erosive esophagitis and other mucosal abnormalities was excluded by means of upper endoscopy performed as off-therapy in one of the above-mentioned centers, within 6 months prior to the initial visit [20].

The patients were sub-grouped through pathophysiological examination performed by means of MII-pH as follows: (1) non-erosive reflux disease (NERD) patients: abnormal acid exposure time (AET); (2) functional heartburn (FH) patients: normal AET and total number of reflux events, absence of correlation between reflux events and symptoms over a 24 h MII-pH recording (SI and SAP) and absence of symptom relief during a previous proton pump inhibitor treatment.

2.4. MII-pH monitoring analysis

All tracings were blindly re-analyzed by expert observers (AT, NdB), with previous experience of analyzing at least 1000 tracings and performing at least 200 MII-pH monitoring instances/year. As the present study was conducted on subjects eating a Mediterranean diet, assessing normal MII-pH values referred to Italian normal values [21]. Impedance and pH data were used to determine the number and type of reflux episodes as well as an acid exposure time (AET, reflux percent time) in each patient. In particular, distal esophageal AET was defined as the total time with pH < 4, divided by the total time of monitoring. Then, a percent time lower than 4.2% with pH < 4 over 24 h, was considered as normal. In patients with CAAG the median gastric pH too was calculated. Reflux episodes were characterized on the basis of their chemical (i.e. acid vs. non-acid) and physical (i.e., liquid, gaseous and mixed-gaseous) composition, according to the Porto classification [22]. As weakly alkaline refluxes are very infrequent, they were merged with weakly acidic refluxes and considered as NA reflux. Only liquid and mixed liquid-gas reflux episodes according to impedance changes were included in the analysis. Proximal reflux was considered as reflux reaching a 15-cm impedance site [21,23]. In each patient, SI and SAP were automatically calculated by software. Only the association between the principal symptom reported by the patient and Ac and NA reflux was reported. SI and SAP were defined according to Wiener et al. and Weusten et al., respectively [24,25] and considered as positive when $\geq 50\%$ and when ≥ 95 , respectively.

The PSPW index, previously described by Frazzoni et al. [11], was manually calculated and defined as the number of refluxes followed within 30 s by a swallow-induced peristaltic wave divided by the number of total refluxes. The MNBI value (in Ohm) was assessed through the same channel (5 cm above the LES) during the overnight rest, at three timepoints (around 1.00 a.m., 2.00 a.m., 3.00 a.m.). In particular, we selected 10 min around each timepoint avoiding swallows, refluxes and pH drops. In fact, as previously

described, short nocturnal time measurements of MNBI are reliably representative of long-period measurements [12–14].

2.5. Statistical analysis

The Kolmogorov–Smirnov test was used to assess data normality. The logarithmic transformation was applied to skewed variables in order to approximate a normal distribution. Statistical tests used to compare patient groups included: ANOVA for differences in mean values, and Kruskal–Wallis test for skewed variables with Bonferroni correction for multiple comparisons (post-hoc analysis).

For each impedance-pH parameter the overall ability to diagnose GERD was assessed by ROC analysis with the 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 cut-off and used to calculate sensitivity and specificity. The correlation between the PSPW index or MNBI with the total number of reflux events (Ac and NA reflux) was assessed with Pearson's coefficient. A p-value <0.05 was considered statistically significant. The data are presented as mean ± standard deviation (SD) or median with 95% confidence interval (95% CI). The analyses were performed using SPSS (version 21, IBM Corp., Armonk, NY).

2.6. Ethical consideration

All the subjects gave their written informed consent. The study was approved by the Institutional Review Boards of the participating centers.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the three groups of patients are shown in Table 1.

As expected, female patients were prevalent among in the CAAG (62%) and FH (76%) groups. No differences regarding age and Body Mass Index (BMI) were evidenced.

Nineteen out of the 24 CAAG patients (79%) reported these symptoms: regurgitation (9 patients), epigastric pain (5), chest pain (2), heartburn (2) and dyspepsia (1). Endoscopy did not show any esophageal mucosal break. By means of MII-pH monitoring, GERD was confirmed in all the CAAG patients as follows: 2 patients with AET >4.2%, 20 with a total reflux number >54, 14 with a positive SI and/or SAP.

Table 2
Esophageal impedance and pH characteristics in the three group of patients.

	CAAG (n=24)	NERD (n=25)	FH (n=25)	p
AET tot (% pH <4)	1.5 ± 2	10 ± 5.1	0.6 ± 0.6	0.0001*
CAAG vs. NERD and FH vs. NERD p <0.001; CAAG vs. FH p > 0.05				
Total reflux (no.)	66 ± 20	73 ± 30	24 ± 7	0.0001*
CAAG vs. FH and NERD vs. FH p <0.001; CAAG vs. NERD p > 0.05				
Acid (no.)	11 ± 10	48 ± 20	10 ± 5	0.0001*
CAAG vs. NERD and FH vs. NERD p <0.001; CAAG vs. FH p > 0.05				
Non-acid (no.)	54 ± 20	25 ± 18	13 ± 5	0.0001*
p <0.05 in the all pairwise comparison				
Proximal reflux (no.)	25 ± 14	30 ± 20	9 ± 4	0.0001*
CAAG vs. FH and NERD vs. FH p <0.001; CAAG vs. NERD p > 0.05				
PSPW index	27 ± 9	27 ± 7	71 ± 6	0.0001*
CAAG vs. FH and NERD vs. FH p <0.001; CAAG vs. NERD p > 0.05				
MNBI (Ohm)	2228 ± 515	971 ± 180	3889 ± 728	0.0046*
p <0.001 in the all pairwise comparison				

AET: acid exposure time; PSPW: post-reflux swallowed inducing peristaltic wave; MNBI: mean nocturnal baseline impedance. Continuous variables shown as mean ± standard deviation.

* p significant when <0.05.

Table 1
Baseline characteristics in the three groups of patients.

	CAAG (n=24)	NERD (n=25)	FH (n=25)	p
Male/female	9/15 (62%)	15/10 (40%)	6/19 (76%)	0.034*
Mean age	58 ± 14	54 ± 15	53 ± 9	0.619
Mean BMI	23 ± 3	25 ± 3	24 ± 4.0	0.321
Symptoms	19 (79%)	25 (100%)	25 (100%)	N/A
AET > 4.2%	2	25	0	N/A
Total no. reflux > 48	20	22	0	N/A
SI/SAP positive	14	19	0	N/A

CAAG: chronic autoimmune atrophic gastritis; NERD: non-erosive reflux disease; FH: functional heartburn; BMI: body mass index; AET: acid exposure time; SI: symptom index; SAP: symptom association probability. Categorical variables shown as number of events and percentage. Continuous variables shown as mean ± standard deviation.

* p significant when <0.05.

All the NERD patients were referred for heartburn and MII-pH monitoring showed an AET >4.2% in all of them; 22 also had a total reflux number >54 and 19 had a positive SI and/or SAP.

All the patients from the FH group showed normal MII-pH values (AET and number of reflux episodes) and no correlation between symptoms and reflux events was shown.

3.2. MII-pH monitoring parameters

The main MII-pH monitoring parameters for the three groups are reported in Table 2.

As expected, the mean AET was significantly higher for NERD patients (10 ± 5.1%) than for CAAG (1.5 ± 2%) and FH patients (0.6 ± 0.6%) (p = 0.0001). The total mean number of reflux events was similar between the CAAG group (66 ± 20) and the NERD one (73 ± 30), but significantly higher in comparison with the FH patients (24 ± 7) (both with p = 0.0001). Non-acid reflux episodes were more common in patients with CAAG, whereas acid reflux events were more common in those with NERD (Table 2). The mean number of refluxes reaching a 15-cm impedance site was significantly lower in patients with FH but comparable between the CAAG and NERD group (Table 2). The mean intra-gastric pH of the patients with CAAG was 6.0 (range 4.5–7.0).

Intriguingly, the MNBI mean value was significantly lower for the NERD group (mean <1000 Ohm) than for the CAAG group (mean >2000 Ohm) and in FH (>3000 Ohm) (p = 0.0046). Finally, the mean PSPW index was similarly lower in patients with CAAG (25 ± 13.8%) and NERD (27.2 ± 7.1%) than in those with FH (70.9 ± 6.1%) (p = 0.0001).

The ROC analysis for both the PSPW index and MNBI was carried out and showed a very high AUC value for both parameters: 0.981

Table 3
Results from ROC analysis (best cut-off, sensitivity, specificity, AUC) for both PSPW and MNBI for GERD diagnosis.

	Best cut-off	AUC	Sensitivity	Specificity
MNBI (Ohms)	2934	0.960	88%	80%
PSPW (%)	60	0.981	96%	100%

AUC: area under the curve; PSPW: post-reflux swallowed-induced peristaltic wave; MNBI: mean nocturnal baseline impedance.

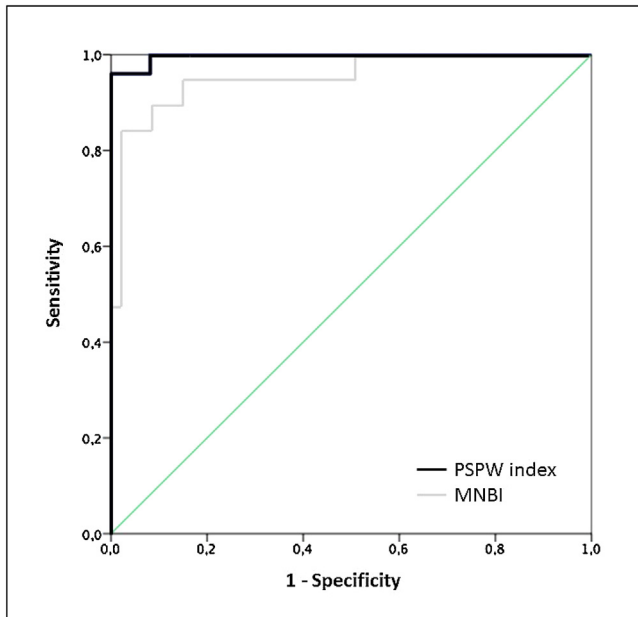


Fig. 1. ROC curves. The black line represents the AUC of PSPW index (0.981) and the grey line represents AUC of MNBI (0.960).

(PSPW index) and 0.960 (MNBI). The results are reported in Table 3 and graphically in Fig. 1.

Moreover, a strong linear inverse correlation between the PSPW index and all reflux types (total, Ac, and NA) was observed ($p < 0.05$). On the other hand, MNBI showed a strong inverse linear correlation with acid reflux and total reflux events ($p < 0.05$) but not with NA reflux events ($p = 0.196$). These analyses are graphically reported in Fig. 2 (PSPW index) and Fig. 3 (MNBI).

4. Discussion

This study evaluated whether reflux-related factors beyond acid exposure may influence the value of two novel parameters, i.e., mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave (PSPW) index. This was achieved by comparing three groups of patients with specific clinical and pH-impedance characteristics: GERD and CAAG, with prevalent non-acid reflux events; NERD, with prevalent acid reflux events and FH with normal reflux events.

As recently reported by Tenca et al. [3], the GERD and CAAG groups present a specific pH-impedance pattern due to the pathophysiology of the disease: (i) increased median intra-gastric pH; (ii) increased number of refluxes, being NA ones more common; (iii) normal AET. Thus, this study shows that MNBI and PSPW index are affected not only by acid reflux, but also by non-acid one. Furthermore, the PSPW index is useful to discriminate between patients with gastro-esophageal reflux disease (GERD) with normal/abnormal AET and functional heartburn (FH).

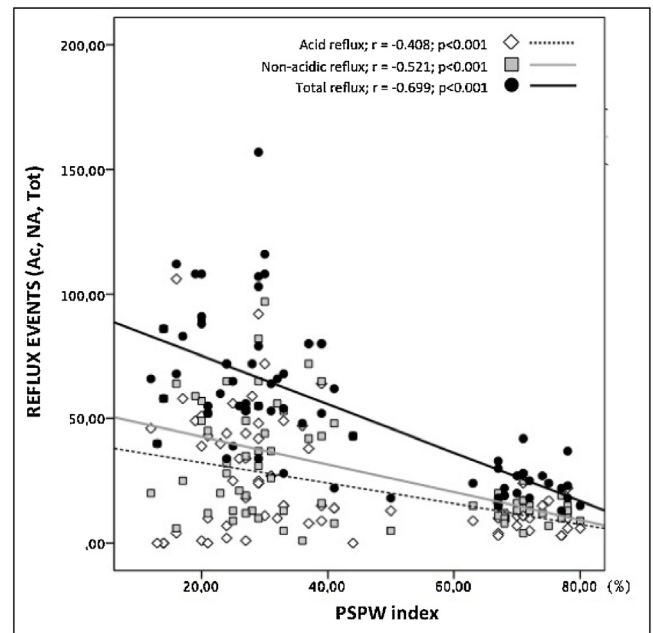


Fig. 2. Linear correlation between acid, weakly-acidic, weakly alkaline and total reflux events and PSPW index with calculation of Pearson r and p value. PSPW, post reflux swallowed induced peristaltic wave; Ac, acid reflux; NA, non-acidic reflux; Tot, total number of reflux events.

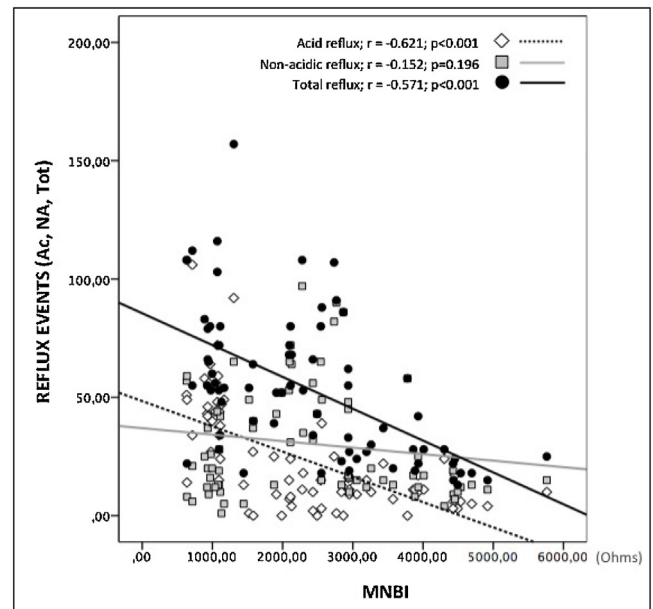


Fig. 3. Linear correlation between acid, weakly-acidic, weakly alkaline and total reflux events and MNBI with calculation of Pearson r and p value. MNBI, mean nocturnal baseline impedance; Ac, acid reflux; NA, non-acidic reflux; Tot, total number of reflux events.

A crucial point is how to diagnose GERD in patients with CAAG, as such patients have low/absent gastric acid secretion and, consequently, absent gastric acid pocket and low AET. The total number of reflux events may be considered as a well-defined parameter of GERD: Pritchett et al. [26] compared on-therapy MII-pH vs. off-therapy wireless-pH monitoring results in the same group of patients: they showed that an abnormal number of reflux events on therapy is a strong predictor of abnormal AET off therapy. They

showed that nearly all (93%) of the patients with an abnormal number of reflux events during on-PPI MII-pH had abnormal AET when studied by wireless-pH monitoring off therapy. Furthermore, Frazzoni et al. [12] showed in a large series of patients, evaluated off-PPI, that AET and the total number of reflux events had overlapping ROC curves with similar sensitivity and specificity in diagnosing GERD. In line with these results, Frazzoni et al. [27] used the on-PPI total number of reflux events to select PPI-refractory GERD patients for laparoscopic fundoplication, with diagnosis accuracy confirmed by an objectively-documented positive 3-year surgical outcome. Finally, the number of total refluxes is unaffected by PPI therapy [28]. Summing up the results of these studies, one can conclude that a higher than normal number of total refluxes represents a marker of GERD.

In a recent study Frazzoni et al. [29] have showed that, in three different groups of patients with refractory reflux esophagitis (RRE), healed reflux esophagitis (HRE) and NERD, as evaluated by on-PPI treatment, the clear majority of reflux events were weakly acidic and neither AET nor acidic reflux events could distinguish RRE from HRE and NERD. This finding suggests that the persistence of esophageal mucosal breaks during PPI treatment cannot be ascribed to higher levels of esophageal acid exposure. The results of the present study show that MNBI and the PSPW index are strong predictors of GERD. MNBI and the PSPW index have been recently reported as capable of improving the diagnostic yield of the MII-pH monitoring of patients with GERD, reliably discriminating among patients with GERD, NERD, and esophageal hypersensitivity [12]. Both parameters can be easily calculated during the visual analysis of tracings and they have high reproducibility [12]. Interestingly, we have observed that MNBI and the PSPW index were influenced not only by acid but also by non-acid reflux. Esophageal baseline impedance is a well-known marker, evaluating mucosal integrity [30]. Similarly, Kessing et al. [31] showed that patients with GERD had lower baseline impedance when compared with healthy volunteers and also that patients with erosive disease had a lower baseline impedance than those with symptomatic GERD without esophageal erosion [31]. The acid has been reported being the main determinant of mucosal integrity associated with low BI [31–33]. Moreover, three different studies have described an inverse correlation between MNBI and AET [12,13,31]. Kessing et al. described that baseline impedance values significantly increase after PPI therapy in patients with GERD [31]. However, in a recent study, Frazzoni et al. [34] have concluded that NA reflux events play a major role in the pathogenesis of PPI-resistant GERD, thus proposing their involvement in symptom generation. The precise pathophysiological mechanisms accounting for these observations were not clarified. However, according to other recent studies, activated pepsins may represent the most relevant determinant to deserve investigation [35,36]. Indeed, pepsins activation occurs at $\text{pH} < 4.5$, but their proteolytic activity is maintained up to $\text{pH} 5.5$ and denaturation occurs at $\text{pH} > 7$ [37]. However, the components of non-acid refluxate influencing mucosal integrity need evaluation through further studies. Our data showed that the PSPW index was similar in patients affected by GERD independently of esophageal acid exposure, but highly different in those patients with functional complaints. Intriguingly, the PSPW index did not differ between NERD and GERD-CAAG patients. This finding confirms that esophageal chemical clearance is elicited by both acid and non-acid refluxes, the latter representing the majority of reflux episodes when gastric acid secretion is reduced as occurs during PPI therapy [11] and in CAAG. Accordingly, the diagnostic power of the PSPW index is unaffected by medical or surgical therapy [11]: this suggests that impaired chemical clearance can be a primary pathophysiological mechanism of GERD [11]. Thus, the PSPW index appears to be a useful parameter to detect patients with GERD, irrespective of the refluxate pH. The ROC analysis showed that both

PSPW and MNBI are very useful in diagnosing GERD patients and in differentiating these patients from those with FH. Our results have showed that the PSPW index and MNBI were similarly affected by acid and NA reflux events. In this regard, some different studies have recently showed that MNBI and the PSPW index can be able to distinguish patients with GERD (NERD and hypersensitive esophagus) from patients with FH [29,38]. Differentiating NERD and FH patients has always presented a challenge to clinical practice [34]. In our study, GERD patients (NERD and GERD-CAAG) had lower MNBI and PSPW index than FH patients. This finding strongly suggests that these parameters together are useful in distinguishing between patients with GERD and patients with FH. Recently, Frazzoni et al. [12] have shown that MNBI and the PSPW index together have the highest sensitivity in diagnosing GERD, by allowing a clear-cut differentiation among GERD patient subgroups (i.e., ERD, NERD, hypersensitive esophagus) in comparison with traditional pH-impedance parameters (i.e., AET and total number of refluxes). Martinucci et al. and de Bortoli et al. have also demonstrated that MNBI may also predict the response-to-PPI-treatment in patients classified as FH according to standard MII-pH parameters [13,14]. By means of ROC analysis, the best cut-off values for the PSPW index and MNBI were $<61\%$ and $<2292 \text{ Ohm}$, respectively [12]. Of notice, in our study the mean MNBI was 971 Ohm in NERD patients and 2228 Ohm in GERD-CAAG patients, whereas the PSPW index resulted as significantly decreased in both groups (about 27%). The MNBI threshold is similar to the value reported by Kandulski et al. [33]. However, an international consensus on esophageal BI values is warranted in the near future.

This study comes with some limitations, including the retrospective design and the relatively small sample size of the three groups.

In terms of acid exposure, we decided to evaluate two heterogeneous groups: NERD and CAAG patients. The first NERD group has a classic GERD (abnormal AET, high number of reflux events); on the other hand, the second group is characterized by having reflux, as demonstrated by a high number of reflux events, but normal AET because of low gastric acid secretion as a consequence of gastric atrophy. Such CAAG patients may present with GERD and reflux-related symptoms as well. Evaluating MII-pH parameters in NERD and CAAG patients can be considered quite similar to comparing patients with GERD off and on PPI therapy, the main difference being the acid exposure. Accordingly, CAAG patients cannot have acid in the fundus as well as acid in the esophago-gastric acid pocket and their reflux events are non-acid. The strongest result of our study is that both the PSPW index and MNBI were able to differentiate the patients with acid and non-acid GERD (NERD and CAAG) from those with FH. We observed that there is a very strong inverse linear relationship between the PSPW index and reflux events (total, acid and non-acidic; $p < 0.001$) and MNBI resulted affected by both the number of acid refluxes and the total number of refluxes ($p < 0.001$). In line with our results, Frazzoni et al. [29] have more recently showed that during on-therapy impedance-pH monitoring, the PSPW index and MNBI were significantly lower in all the evaluated GERD patient subgroups (RRE, refractory reflux esophagitis and HRE, healed reflux esophagitis) in comparison to FH patients and, differently from the other impedance-pH variables, they were significantly lower in RRE than in HRE and NERD: these results thus pointing out to the pathophysiological soundness and the diagnostic value of both these novel impedance parameters for PPI-refractory heartburn patients tested while on PPI therapy. Our results have showed similar results in patients with CAAG and NERD (this is the really new data) instead of patients with GERD evaluated on and off PPI treatment.

5. Conclusions

Nowadays the axiom “no acid–no reflux” [39,40] is not sufficient to account for the complex pathophysiology of reflux especially in patients with low gastric acid output (CAAG patients and heartburn patients on PPI). The esophageal impedance parameters MNBI and PSPW index are confirmed to be really useful in order to distinguish patients with GERD from patients with FH: they may really improve the diagnostic yield of impedance–pH monitoring.

Conflict of interest

None declared.

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