TITLE: Lack of improvement of impaired chemical clearance characterizes PPI-refractory reflux-related heartburn

AUTHORS:
Marzio Frazzoni[1], Leonardo Frazzoni[2], Salvatore Tolone[3], Nicola de Bortoli[4], Vincenzo Savarino[5] and Edoardo Savarino[6]

AFFILIATIONS
1 Digestive Pathophysiology Unit, Baggiovara Hospital, Modena, Italy.
2 Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
3 Department of Surgery, Division of Surgery, Second University of Naples, Naples, Italy.
4 Department of Translational Research and New Technology in Medicine and Surgery, Division of Gastroenterology, University of Pisa, Pisa, Italy.
5 Department of Internal Medicine (DIMI), Division of Gastroenterology, University of Genoa, Genoa, Italy.
6 Department of Surgery, Oncology and Gastroenterology, Division of Gastroenterology, University of Padua, Padua, Italy.

Corresponding Author:
Marzio Frazzoni, Digestive Pathophysiology Unit,
Baggiovara Hospital, Modena, Italy.
E-mail: marziofrazzoni@gmail.com

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- The reasons for refractoriness of reflux-related heartburn to PPI therapy have not yet been fully elucidated.
- Impedance-pH monitoring, allowing thorough assessment of reflux during PPI therapy, represents a valuable test to investigate the mechanisms of PPI refractoriness.

WHAT IS NEW HERE

- Overall, gastric acid secretion and acid reflux burden are similarly suppressed in patients with PPI-refractory and PPI-responsive reflux-related heartburn.
- Severe impairment of chemical clearance is the only independent risk factor for heartburn refractoriness to PPI therapy.
- Lack of improvement of impaired chemical clearance during acid suppressive therapy distinguishes PPI-refractory from PPI-responsive reflux-related heartburn.

CONFLICT OF INTEREST

Guarantor: Marzio Frazzoni, MD.

Specific author contributions: MF: study concept and design; collection, analysis, and interpretation of data; drafting of the manuscript. LF: analysis and interpretation of data; drafting of the manuscript. ST, ES: collection, analysis, and interpretation of data; critical revision of the manuscript. NDB, VS: analysis and interpretation of data; critical revision of the manuscript.

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ABSTRACT

Objective: Heartburn is the most specific symptom of reflux disease and is highly responsive to proton pump inhibitor (PPI) therapy. Some patients do not respond to PPIs, but mechanisms of refractoriness have not yet been fully elucidated. Impedance-pH monitoring, allowing comprehensive on-therapy assessment of reflux, represents a valuable test to investigate PPI refractoriness.

Methods: Prospective multicenter study comparing endoscopy-negative patients with PPI-refractory and PPI-responsive heartburn. Reflux disease was demonstrated by off-PPI impedance-pH monitoring and mechanisms of refractoriness were studied with on-PPI impedance-pH monitoring. Assessment of impedance-pH tracings comprised conventional parameters, post-reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI).

Results: Sixty-four patients entered the study, 32 with PPI-refractory and 32 with PPI-responsive heartburn. On PPI, median percentage gastric and esophageal acid exposure time and number of acid refluxes did not differ between the two groups; conversely, number of total and weakly acidic refluxes and percentage bolus exposure were significantly higher while PSPW index and MNBI were significantly lower in PPI-refractory cases. At multivariate logistic regression analysis, PSPW index was the sole independent risk factor for PPI refractoriness (OR 1.082, 95% CI 1.022–1.146, p=0.007). Comparing off- and on-PPI parameters, median PSPW index did not change in PPI-refractory patients (24% vs. 26%, P = 0.327) but increased significantly in PPI-responsive cases (29% vs. 46%, p< 0.001).

Conclusions: Lack of improvement of impaired chemical clearance is a major determinant of PPI refractoriness. Timely post-reflux salivary swallowing represents a key defensive mechanism and a potential target for future treatment modalities in PPI-refractory reflux-related heartburn.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is currently defined as reflux of gastric contents into the esophagus leading to troublesome symptoms and/or complications [1]. Heartburn represents the most specific GERD symptom and the most responsive to acid suppression by proton pump inhibitor (PPI) therapy [2]. In clinical practice, heartburn relief with PPI therapy can be used to confirm GERD [1, 2]. Unfortunately, some patients do not achieve heartburn remission even with high dosages of PPIs [3]. In these cases, demonstration that the symptom is reflux-related is warranted but endoscopy is most often normal, so that reflux monitoring is required [3]. Impedance-pH monitoring, providing a comprehensive assessment of reflux independently of the pH of refluxate, allows to distinguish reflux-related from reflux unrelated, i.e., functional heartburn [4] and also to investigate the mechanisms of PPI refractoriness [2, 3]. By impedance-pH monitoring it has long been recognized that PPIs transform the majority of acid refluxes into weakly acidic refluxes [5, 6]. Weakly acidic refluxes are noxious for the esophageal mucosa, since the proteolytic activity of pepsins is maintained up to pH 6.0 [7] and healing of mucosal damage is inhibited at pH <6.5 [8]. Weakly acidic refluxes comprise the vast majority of symptom-associated refluxes in PPI-refractory GERD and are nearly abolished by successful laparoscopic fundoplication [9], implying that they have some role in PPI resistance. However, weakly acidic refluxes represent the majority of on-PPI reflux events both in non-responsive and responsive reflux-related heartburn [5, 6]: hence, it seems that other factors are implicated in the pathogenesis of PPI refractoriness. Actually, the mechanisms of different heartburn responses to PPIs have not yet been fully elucidated [3].

Two novel impedance-pH parameters, namely the post-reflux swallow-induced peristaltic wave (PSPW) index, which evaluates esophageal chemical clearance [10], and the mean nocturnal baseline impedance (MNBI), which assesses esophageal mucosal integrity [11, 12], have been shown to increase our ability to diagnose

GERD in recent multicenter studies [13–16], affording significant diagnostic gain in patients evaluated off as well as on PPI therapy.

Analysis of PSPW index and MNBI during acid-suppressive therapy as compared with off-therapy findings could contribute to clarify the pathogenesis of PPI refractoriness.

Aim of the present study was to clarify the mechanisms of PPI-refractory reflux-related heartburn by means of on-therapy impedance-pH monitoring with analysis of conventional and novel parameters.

METHODS

This prospective multicenter study included patients evaluated in Italian tertiary care centers. Patients were referred from their caring physicians for possible antireflux surgery because of PPI refractory heartburn or PPI-responsive heartburn with persistent extraesophageal syndromes. The study was carried out in accordance with the Helsinki Declaration and current recommendations [3]; since patients were investigated for clinical reasons and were not exposed to any additional interventions for the study purpose, in accordance with Italian law formal medical ethical assessment was not required. A signed informed consent was always obtained before clinical investigations. A validated structured questionnaire [17], consisting in a four-grade Likert-type scale scoring system, administered by a senior investigator and aided by a patient self-assessed visual-analog scale [12], was used to evaluate esophageal and dyspeptic as well as extraesophageal symptoms (cough, asthma, and laryngeal symptoms including hoarseness, globus, and throat clearing). Symptom scores were:
0, none; 1, mild/occasional; 2, moderate/frequent; 3, severe/constant.
Symptoms were considered troublesome for score 2 or 3. Previous esophagogastric surgery, Sjogren syndrome, scleroderma, as well as dysphagia, chest pain, and dyspeptic symptoms dominating the clinical picture constituted exclusion criteria. All patients underwent esophagogastroduodenoscopy at our centers after 4-week PPI withdrawal (antacids permitted). Patients with detection of erosive reflux esophagitis or Barrett's esophagus were excluded. Hiatal hernia was defined as a distance between the diaphragmatic hiatus and the gastroesophageal junction >2 cm.
Endoscopy-negative patients underwent off-PPI impedance-pH monitoring, always preceded by conventional or high-resolution esophageal manometry to locate the lower esophageal sphincter (LES) and exclude major esophageal motility disorders, i.e., achalasia, esophago-gastric junction outflow obstruction/impaired LES relaxation, absent contractility, and hypercontractility [18, 19]. The impedance-pH probe allowed

monitoring changes in intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm above the upper border of the manometrically identified LES. In addition, pH was monitored at 5 cm above and 10 cm below the upper LES border. Impedance-pH tracings were assessed by means of manual analysis, consisting in evaluation of 2-min time windows, with zooming whenever deemed necessary. Mealtimes were excluded. Liquid and liquid– gas reflux events were distinguished into acid (nadir pH < 4.0), weakly acidic (nadir pH between 4.0 and 7.0), and weakly alkaline (nadir pH not below 7.0). The percentage gastric acid (pH < 4.0) exposure time (GAET), the percentage esophageal acid (pH < 4.0) exposure time (EAET), the number of totals, acid, weakly acidic, and weakly alkaline refluxes, as well as the percentage bolus exposure were calculated by the Autoscan software (Sandhill Scientific, Inc; Highland Ranch, CO) after manual analysis. Symptom-reflux association was evaluated by means of symptom-association probability (SAP) and symptom index (SI): positive SAP and SI were defined by more than 95% and by more than 50%, respectively, of heartburn episodes following reflux events within 2 min [20]. A PSPW was defined as an antegrade 50% drop in impedance occurring within 30 s after a reflux event, originating in the proximal impedance channels, reaching the most distal impedance channel, and followed by at least 50% return to the baseline. Dividing the number of PSPWs by the number of reflux events, the PSPW index was obtained [10]. MNBI was assessed from the most distal impedance channel during nighttime recumbent period; three 10-min time periods (around 1.00 am, 2.00 am, and 3.00 am) were selected and the mean was calculated, with avoidance of time periods including swallows, refluxes and pH drops [11]. According to receiver-operating-characteristic (ROC) curves, the optimal decision-making analysis tool, derived from 289 GERD patients and 50 healthy controls eating a standard Mediterranean diet [13], EAET, PSPW index, and MNBI were regarded as abnormal when >3.2%, <61%, and <2292 Ohms, respectively [13]. Impedance-pH criteria for considering heartburn as reflux-related comprised off-PPI abnormal EAET and/or concordant SAP/SI positivity and/or abnormal values of both PSPW index and MNBI with positive PPI response [13, 14, 16]. Patients with reflux-related heartburn

then underwent on-PPI impedance-pH monitoring during double-daily standard dosage of PPI started from at least 8 weeks after previous off-therapy testing, preceded by symptom reevaluation by the same senior investigator aided by patient self-assessed visual analog scale: symptom relief was defined by a >50% Likert-type scale scoring decrease (0 if the baseline score was 2 and 0 or 1 if the baseline score was 3). Cases with troublesome (score 2 or 3) heartburn persisting after 8-week high-dosage PPI constituted the PPI-refractory group, while those with heartburn relieved by PPI therapy constituted the PPI-responsive group.

Statistics

For sample size calculation, we considered the PSPW index since this parameter showed the greatest area under the curve at ROC analyses [13–16] and used a significance level of 5% and a power of 90%. In order to allow inter-group on-PPI detection of at least 9% difference and assuming a 10% standard deviation [15], we calculated that 27 cases in each group were required. Continuous variables are presented as median and interquartile range (IQR). Differences between groups were analyzed with the Mann–Whitney test for continuous variables, and the $\chi 2$ test or the Fisher exact test for categorical variables. Impedance-pH parameters independently associated with PPI refractoriness were identified by means of multivariate logistic regression analysis. Off- and on-PPI impedance-pH parameters were compared using the Wilcoxon rank sum test. IBM SPSS, Version 22 (IBM Corp., Armonk, NY, USA) was used. Significance was set at $P < 0.05$.

RESULTS

Between March 2015 and June 2017, 64 patients were included in the study (Fig. 1), 32 with PPI-refractory heartburn and 32 with PPI-responsive heartburn but persistent extraesophageal symptoms (Table 1). The two groups were well comparable for gender, age, BMI, rates of hiatal hernia and of abnormal off-PPI impedance-pH variables (Table 2); 53 of 64 (83%) patients had abnormal EAET while six patients (9%) with normal EAET had concordant SAP/SI and PSPW index/MNBI positivity; five patients (8%) with history of PPI-dependent heartburn, recurring at PPI withdrawal and again PPI-suppressed, had normal EAET and omitted to register heartburn during the 24-h study but concordant positivity of PSPW index and MNBI confirmed that PPI-responsive heartburn was reflux related [14, 16]. Baseline off-therapy median values of impedance-pH and manometric parameters did not differ between the two groups (Table 3).

Patients were then prescribed a double-daily standard PPI dose: 54 received esomeprazole (25 in the PPI-refractory group), five rabeprazole (three in the PPI-refractory group), three lansoprazole (two in the PPI-refractory group), and two pantoprazole (both in the PPI-refractory group). On PPI therapy, reevaluation of symptoms confirmed persistence of troublesome heartburn in the PPI-refractory group and heartburn abolition in the PPI-responsive group. Six of 32 (19%) and 0 of 32 patients had abnormal EAET in the PPI-refractory and PPI-responsive group, respectively ($P = 0.024$). Median GAET, EAET, and acid refluxes did not differ between the two groups, whereas total refluxes, weakly acidic refluxes, and bolus exposure were significantly higher and PSPW index and MNBI were significantly lower in PPI-refractory cases Comparing off- and on-PPI impedance-pH findings, GAET, EAET, and acid refluxes decreased significantly, whereas weakly acidic refluxes and MNBI increased significantly both in PPI-refractory and in PPI-responsive (Table 5) cases. Contrarily, PSPW index increased significantly in PPI-

responsive but not in PPI-refractory patients. Fig. 2 shows individual and median values of PSPW index in PPI-refractory and PPI-responsive cases, both off and on PPI.

DISCUSSION

to PPI therapy. Some patients do not respond even to high-dosage PPI but the mechanisms of different responses have not yet been fully elucidated. Extraesophageal symptoms can be associated with heartburn but response to PPI therapy is much less predictable [2]. Impedance-pH monitoring is advised for PPI-refractory typical and atypical reflux symptoms to confirm GERD and document the mechanisms of PPI refractoriness before advising antireflux surgery [3]. Since extraesophageal symptoms often persist after antireflux surgery [21], differently from heartburn [9, 15], patients with PPI-responsive heartburn but refractory respiratory symptoms must be carefully evaluated with on-PPI impedance-pH monitoring because only uncontrolled reflux may suggest surgery [1–3]. On-PPI impedance-pH comparison of these patients to those with PPI-refractory heartburn gives the opportunity to clarify the mechanisms of heartburn refractoriness to PPI therapy.

In this prospective multicenter study, 32 patients with endoscopy-negative, PPI-refractory reflux-related heartburn were investigated with on-therapy impedance-pH monitoring and compared to 32 patients with endoscopy-negative, PPI-responsive reflux related heartburn but persistent extraesophageal symptoms. The two groups were well comparable for demographic characteristics, as well as for baseline off-PPI endoscopic, manometric and impedance-pH findings. Overall, on-PPI median GAET, EAET, and acid refluxes did not differ between the PPI-refractory and the PPI-responsive heartburn group, while persistent abnormal EAET values were detected in a minority of PPI-refractory cases. Total refluxes, weakly acidic refluxes, and bolus exposure were significantly higher, while PSPW index and MNBI were significantly lower in PPI-refractory as compared to PPI-responsive cases. At multivariate logistic regression analysis, PSPW index proved to be the sole independent risk factor for heartburn refractoriness to PPI therapy. Comparing off- and on-PPI impedance-pH findings, the PSPW index did not change in PPI-refractory patients, whereas a significant increase was observed in PPI-responsive cases.

According to our results, refractoriness of reflux-related heartburn to PPI therapy cannot be ascribed to persistent abnormal esophageal acid exposure in most cases. We confirm that PPI therapy transforms the vast majority of reflux events from acidic to weakly acidic [5, 6], and found significantly higher values in the PPI-refractory group. However, neither a higher number of weakly acidic refluxes nor a higher number of total refluxes proved to be an independent risk factor for PPI refractoriness at multivariate logistic regression analysis, suggesting that reflux episodes represent only a trigger but other factors must play a more important role in the pathogenesis of PPI refractoriness.

Low baseline impedance reflects impaired esophageal mucosa integrity, in turn representing a consequence of reflux and a putative mechanism of reflux perception [22]. Baseline impedance can easily and accurately be measured with MNBI [11], which can predict symptomatic response to antireflux therapy [12, 16, 23]. In the present study, MNBI increased significantly during PPI treatment both in PPI-refractory and in PPI-responsive patients. At on-PPI testing, median MNBI was higher than normal in PPI-responsive cases, but lower than normal in PPI-refractory patients, suggesting only partial recovery of mucosal integrity in the latter group.

Hence, ongoing impairment of mucosal integrity can contribute to heartburn persistence during PPI therapy, although not as a primary mechanism since MNBI was not an independent risk factor for heartburn refractoriness to PPIs at multivariate logistic regression analysis. After reflux has occurred, volume and chemical clearance represent a major esophageal defense mechanism [24]. Volume clearance consists of a secondary peristaltic wave, removing the greatest part of the refluxed bolus [25]. However, this mechanism is not sufficient for neutralization of esophageal pH and additional chemical clearance is required [25], consisting of salivary swallow delivering bicarbonate and epidermal growth factor, in turn increasing pH and accelerating mucosal reparative processes. At impedance-pH monitoring, volume and chemical clearance can be assessed with percentage bolus exposure and PSPW index, respectively, the latter assessing early (within 30 s) delivery of swallowed saliva to the

distal esophagus after the end of a reflux episode, i.e., after volume (bolus) clearance has occurred. A low PSPW index stands for impaired chemical clearance, i.e., prolonged contact time of the esophageal mucosa with acid and weakly acidic refluxes [10]. Lower values of PSPW index distinguish PPI-refractory from PPI-healed reflux esophagitis [26] and can predict neoplastic progression in short-segment Barrett's esophagus [27], independently from percentage bolus exposure and also from acid suppression, as measured with on-PPI GAET and EAET [26, 27]. In the present study, percentage bolus exposure was unaffected by acid-suppressive therapy in either PPI-refractory or PPI-responsive patients, in contrast with the PSPW index, which was the sole independent risk factor for PPI refractoriness at multivariate logistic regression analysis. Since PSPW index was unaffected by acid suppression in PPI-refractory heartburn patients but increased significantly in PPI-responsive cases, the lack of improvement of impaired chemical clearance during acid-suppressive therapy appears to represent a key factor in the pathogenesis of PPI-refractory reflux-related heartburn. In other terms, these data show that timely swallowed saliva represents a major defense mechanism against reflux. The workup of a patient with endoscopy-negative reflux symptoms persistent despite PPI therapy is challenging. The first step should be to establish that symptoms are reflux-related by off-PPI pH/impedance-pH monitoring [2, 3]; afterward, on-PPI impedance-pH monitoring should be carried out to clarify the mechanisms of PPI refractoriness [2, 3]. Hemmink et al. [5] evaluated conventional impedance-pH parameters in 30 PPI-refractory patients studied off and on therapy, showing PPI-induced normalization of median EAET. Ribolsi et al. [28] compared off- and on-therapy conventional impedance-pH parameters in 10 PPI-responsive and 10 PPI-refractory patients: on PPI, EAET was normal in all cases and did not differ between the two groups. On PPI, we found abnormal EAET values in few cases only, further suggesting that chances of overcoming PPI-refractoriness with more profound acid inhibition are poor. On the other hand, analyzing the PSPW index, a novel parameter which significantly increases the diagnostic yield of impedance-pH monitoring [13–16], we found that improvement of chemical clearance is the key factor

distinguishing PPI-responsive form PPI-refractory reflux-related heartburn. This could have practical clinical implications: improvement of chemical clearance by stimulation of timely post-reflux salivary swallowing could represent a potential target of novel treatment modalities for PPI-refractory patients, possibly allowing avoidance of antireflux surgery with its well-known side effects [1–3].

In conclusion, our study shows that the main determinant of PPI-refractoriness in patients with reflux-related heartburn is the lack of improvement of impaired chemical clearance, but not inadequate acid suppression. Timely salivary swallowing after reflux events represents a major defensive factor against esophageal mucosa damage induced by acid and weakly acidic refluxes. Improvement of chemical clearance by stimulation of timely post-reflux salivary swallowing could represent a potential 65 P= 0.327 P< 0.001 target of future treatment modalities for patients with PPI-refractory reflux-related heartburn.

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TABLE PAGES

Table 1: Off- and on-PPI symptoms as assessed with a four-grade Likert-type scale scoring system

	OFF PPI	ON PPI
PPI-refractory heartburn (32 cases)	• Severe heartburn (score 3): 15 cases • Moderate heartburn (score 2): 17 cases	• Severe heartburn (score 3): 9 cases • Moderate heartburn (score 2): 23 cases
	Median OFF-PPI heartburn score 2; median ON-PPI heartburn score 2 ($P=0.087$)	
PPI-responsive heartburn with persistent extrae-sophageal symptoms (32 cases)	• Severe heartburn (score 3): 8 cases • Moderate heartburn (score 2): 24 cases	• Mild heartburn (score 1): 2 cases • No heartburn (score 0): 30 cases
	Median OFF-PPI heartburn score 2; median ON-PPI heartburn score 0 ($P<0.001$)	
Cough (17 cases)	• Severe (score 3): 8 cases • Moderate (score 2): 9 cases	• Severe (score 3): 6 cases • Moderate (score 2): 11 cases
Laryngeal symptoms (12 cases)	• Severe (score 3): 2 cases • Moderate (score 2): 10 cases	• Severe (score 3): 1 case • Moderate (score 2): 11 cases
Asthma (3 cases)	• Severe (score 3): 2 cases • Moderate (score 2): 1 case	• Severe (score 3): 2 cases • Moderate (score 2): 1 case

PPI proton pump inhibitor

Table 2: Baseline off-therapy characteristics of 32 patients with PPI-refractory and 32 patients with PPI-responsive endoscopy-negative heartburn

	PPI-refractory	PPI-responsive	*P*
Male gender (*n*) (%)	16/32 (50%)	18/32 (56%)	0.802
Age (years) (median) (IQR)	48 (44–56)	56 (47–62)	0.070
BMI (median) (IQR)	25 (23–27)	25 (24–27)	0.535
Hiatal hernia (*n*) (%)	24/32 (75%)	16/32 (50%)	0.071
Abnormal EAET (*n*) (%)	29/32 (91%)	24/32 (75%)	0.185
Abnormal PSPW index (*n*) (%)	32/32 (100%)	32/32 (100%)	0.999
Abnormal MNBI (*n*) (%)	26/32 (81%)	28/32 (88%)	0.731
Positive SAP (*n*) (%)	21/32 (66%)	13/32 (41%)	0.080
Positive SI (*n*) (%)	23/32 (72%)	15/32 (47%)	0.075

Legend: PPI=proton pump inhibitor; BMI=body mass index; IQR=interquartile range; EAET=esophageal acid exposure time; SAP=symptom association probability; SI=symptom index; PSPW=post-reflux swallow-induced peristaltic wave; MNBI=mean nocturnal baseline impedance

Table 3: Baseline off-therapy impedance-pH and manometry parameters in 32 patients with PPI-refractory and 32 patients with PPI-responsive endoscopy-negative heartburn

	PPI-refractory	PPI-responsive	*P*
GAET (%)	93.4 (87.0–95.3)	94.8 (91.3–96.2)	0.944
EAET (%)	6.2 (4.2–9.9)	5.0 (3.3–8.9)	0.471
Total refluxes (*n*)	53 (39–77)	42 (31–68)	0.053
Acid refluxes (*n*)	46 (33–63)	41 (26–50)	0.076
Weakly acidic refluxes (*n*)	7 (4–13)	3 (1–13)	0.087
Weakly alkaline refluxes (*n*)	0 (0–0)	0 (0–0)	0.992
Bolus exposure (%)	2.3 (2.0–3.2)	1.4 (0.8–2)	0.568
PSPW index (%)	24 (19–31)	29 (20–32)	0.378
MNBI (Ohms)	1321 (889–1861)	1127 (741–1655)	0.214
LES tone (mm Hg)	19.6 (15.1–25.1)	19 (11.9–22.4)	0.324
MDEA (mm Hg)	64.3 (50.7–88.7)	60.3 (47.9–100.2)	0.995

Legend: Data are presented as median and interquartile range, PPI=proton pump inhibitor; GAET=gastric acid exposure time; EAET=esophageal acid exposure time; PSPW=post-reflux swallow-induced peristaltic wave; MNBI=mean nocturnal baseline impedance; LES=lower esophageal sphincter; MDEA=mean distal esophageal amplitude

Table 4: On-therapy impedance-pH parameters in 32 patients with PPI-refractory and 32 patients with PPI-responsive endoscopy-negative heartburn

	PPI-refractory	PPI-responsive	*P*
GAET (%)	29.1 (19.2–45.3)	31.2 (20.8–43.9)	0.833
EAET (%)	0.4 (0.1–1.9)	0.1 (0.0–0.8)	0.190
Total refluxes (*n*)	53 (35–81)	29 (14–47)	0.002
Acid refluxes (*n*)	9 (3–16)	4 (1–9)	0.061
Weakly acidic refluxes (*n*)	34 (17–64)	23 (8–37)	0.018
Weakly alkaline refluxes (*n*)	0 (0–0)	0 (0–0)	0.872
Bolus exposure (%)	2.3 (1.2–5.0)	0.9 (0.4–1.9)	0.008
PSPW index (%)	26 (19–37)	46 (35–51)	<0.001
MNBI (Ohms)	2129 (1615–2742)	2779 (2199–3122)	0.012

Multivariate logistic regression analysis	**Odds ratio (95% CI)**	***P***
Total refluxes	0.995 (0.940–1.053)	0.862
Weakly acidic refluxes	0.997 (0.935–1.063)	0.917
Bolus exposure	0.717 (0.320–1.607)	0.717
PSPW index	1.082 (1.022–1.146)	0.007
MNBI	1.001 (0.999–1.002)	0.098

Legend: Data are presented as median and interquartile range
PPI=proton pump inhibitor; GAET=gastric acid exposure time; EAET=esophageal acid exposure time; PSPW=post-reflux swallow-induced peristaltic wave; MNBI=mean nocturnal baseline impedance; CI=confidence interval.

Table 5: Off- and on-PPI impedance-pH parameters in 32 patients with PPI-refractory and 32 patients with PPI-responsive endoscopy-negative heartburn

	OFF PPI	ON PPI	P
GAET (%)–PPI-refractory	93.4 (87.0–95.3)	29.1 (19.2–45.3)	<0.001
GAET (%)–PPI-responsive	94.8 (91.3–96.2)	31.2 (20.8–43.9)	<0.001
EAET (%)–PPI-refractory	6.2 (4.2–9.9)	0.4 (0.1–1.9)	<0.001
EAET (%)–PPI-responsive	5.0 (3.3–8.9)	0.1 (0.0–0.8)	<0.001
Total refluxes (*n*)–PPI-refractory	53 (39–77)	53 (35–81)	0.652
Total refluxes (*n*)–PPI-responsive	42 (31–68)	29 (14–47)	<0.001
Acid refluxes (*n*)–PPI-refractory	46 (33–63)	9 (3–16)	<0.001
Acid refluxes (*n*)–PPI-responsive	41 (26–50)	4 (1–9)	<0.001
Weakly acidic refluxes (*n*)–PPI-refractory	7 (4–13)	34 (17–64)	<0.001
Weakly acidic refluxes (*n*)–PPI-responsive	3 (1–13)	23 (8–37)	<0.001
Bolus exposure (%)–PPI-refractory	2.3 (2.0–3.2)	2.3 (1.2–5.0)	0.103
Bolus exposure (%)–PPI-responsive	1.4 (0.8–2)	0.9 (0.4–1.9)	0.144
PSPW index (%)–PPI-refractory	24 (19–31)	26 (19–37)	0.327
PSPW index (%)–PPI-responsive	29 (20–32)	46 (35–51)	<0.001
MNBI (Ohms)–PPI-refractory	1321 (889–1861)	2129 (1615–2742)	<0.001
MNBI (Ohms)–PPI-responsive	1127 (741–1655)	2779 (2199–3122)	<0.001

Legend: Data are presented as median and interquartile range.
PPI=proton pump inhibitor; GAET=gastric acid exposure time; EAET=esophageal acid exposure time; PSPW=post-reflux swallow-induced peristaltic wave; MNBI=mean nocturnal baseline impedance.

FIGURE PAGE

Figure 1: Flow diagram for the study. PPI proton pump inhibitor, MII-pH multichannel intraluminal impedance-pH monitoring, EAET esophageal acid exposure time, SAP symptom association probability, SI symptom index, PSPW post-reflux swallow-induced peristaltic wave, MNBI mean nocturnal baseline impedance.

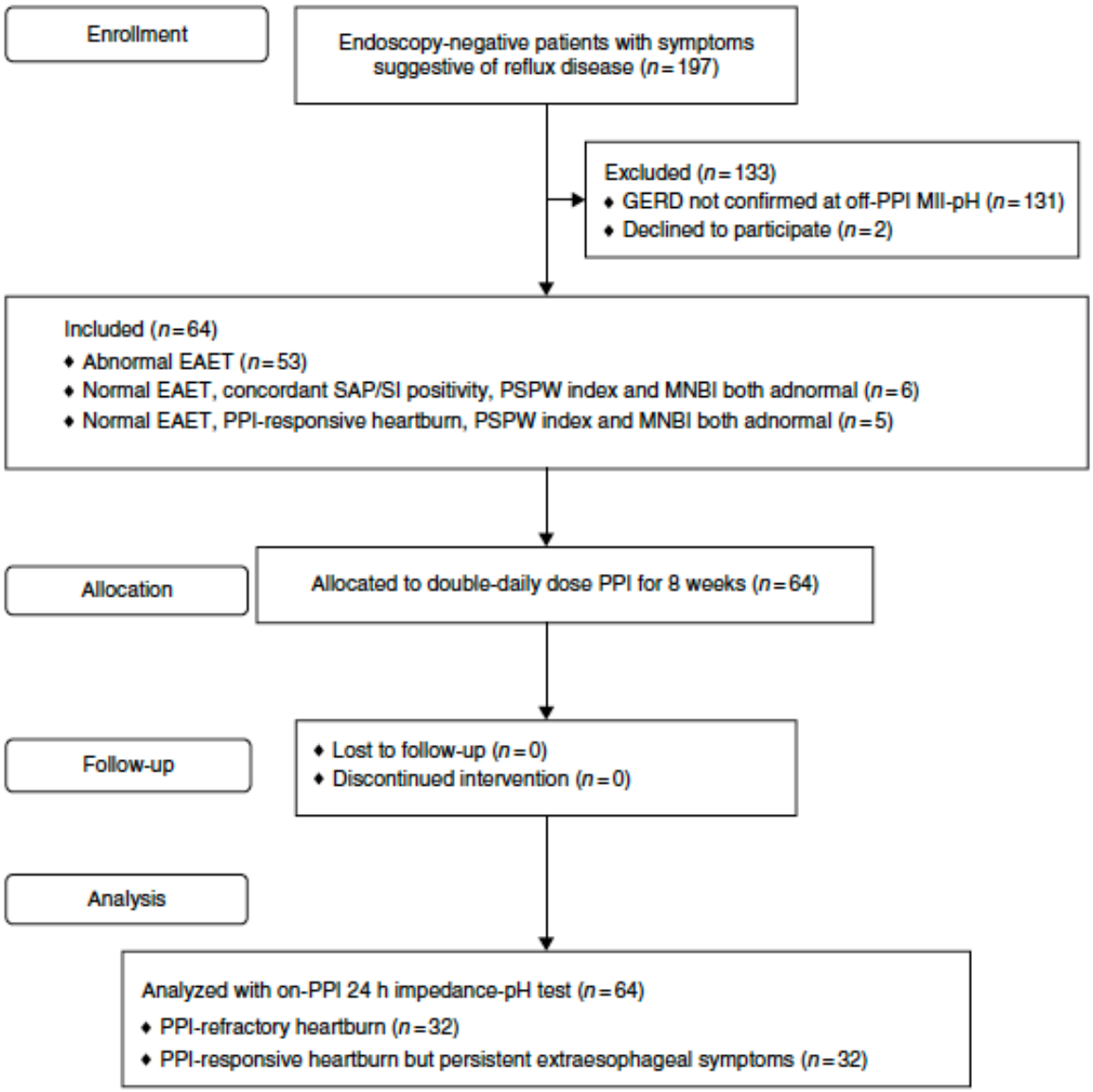

Figure 2: Individual and median values for post-reflux swallow-induced peristaltic wave (PSPW) index in 32 PPI-refractory and 32 PPI-responsive patients with endoscopy-negative reflux-related heartburn, off and on PPI