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REVIEW

Impedance-pH Monitoring for Diagnosis of Reflux Disease: New Perspectives

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Abstract Heartburn is the most specific symptom of gastroesophageal reflux disease (GERD). In clinical practice, heartburn relief by a proton pump inhibitor (PPI) trial does suffice to confirm GERD. However, an objective diagnosis of GERD is required before anti-reflux endoscopic or surgical interventions, independently from PPI response. Thus, since normal findings at upper endoscopy are detected in the majority of patients with heartburn, reflux monitoring is often required. When traditional catheter-based or wireless pH tests are used, reflux episodes are conventionally identified by pH drops below 4.0 units. Combined impedance-pH monitoring has the advantage to provide a comprehensive assessment of both physical and chemical properties of refluxate and the distinction between acid and weakly acidic refluxes, both proven to cause heartburn. Unfortunately, the conventional impedance-pH parameters, namely acid exposure time and number of reflux events, are characterized by suboptimal diagnostic sensitivity, and the reliability of symptom–reflux association indexes remains questionable. Therefore, novel impedance parameters, namely the post-reflux swallow-induced peristaltic wave (PSPW) index and the mean nocturnal baseline impedance (MNBI), have recently been proposed in order to achieve a better diagnostic yield. In fact, they proved to be highly accurate in distinguishing reflux-related from reflux-unrelated heartburn, off- as well as on-PPI therapy. Currently, manual review of impedance-pH tracings is needed because of the modest accuracy of available software tools for automated analysis. PSPW index and MNBI are highly applicable and reproducible, and their calculation requires a few additional minutes during the manual review of impedance-pH tracings. So far, we believe that PSPW index and MNBI are ready for prime time and should become part of the standard analysis of impedance-pH tracings for GERD diagnosis in patients with endoscopy-negative heartburn.

Keywords GERD · NERD · PPI · Impedance-pH monitoring · Esophageal chemical clearance · PSPW index · Esophageal baseline impedance

Abbreviations

AUC	Area under the curve
AET	Acid exposure time
ERD	Erosive reflux disease
FH	Functional heartburn
GERD	Gastroesophageal reflux disease
HE	Hypersensitive esophagus
MNBI	Mean nocturnal baseline impedance
NERD	Non-erosive reflux disease
PSPW	Post-reflux swallow-induced peristaltic wave
ROC	Receiver operating characteristic
SAP	Symptom association probability
SI	Symptom index

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Introduction

Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms and/or complications [1–3] and is the most common chronic upper digestive disorder encountered by the gastroenterologist. Typical GERD is defined by the presence of troublesome heartburn with/without regurgitation [1–3]. Heartburn is the cardinal GERD symptom and consists of a burning sensation in the retrosternal area, whereas regurgitation is defined as the perception of refluxed gastric contents into the mouth [1]. Proton pump inhibitor (PPI) therapy represents the mainstay of medical treatment for typical GERD, with more than 80% of efficacy in healing reflux esophagitis and relieving heartburn [3]. Therefore, in clinical practice heartburn relief by a PPI trial is a reasonable approach to confirm GERD [3].

In the absence of alarm symptoms, diagnostic investigations are recommended in patients with PPI-refractory heartburn and in uninvestigated PPI-responsive cases before endoscopic or surgical anti-reflux interventions [3]. Since endoscopy shows erosive reflux disease (ERD) in less than one-third of patients with heartburn [4], direct reflux monitoring [5], always preceded by esophageal manometry [6], is required in the majority of cases. Most patients with endoscopy-negative heartburn are classified as non-erosive reflux disease (NERD) on the basis of abnormal results at pH or impedance-pH monitoring [4], whereas those with normal results and unsatisfactory response to a PPI trial have been defined as functional heartburn (FH) and considered as a separate entity from GERD [5].

Limitations of pH Monitoring

Reflux is traditionally assessed by means of catheter-based or wireless pH monitoring and identified by pH drops below 4.0 units. The total percentage of time with pH < 4.0, namely the acid exposure time (AET), is considered as the most useful parameter to separate physiologic from pathologic reflux [7]. Unfortunately, the AET normative values reported in different centers range widely from 3.2 to 7.2% [7]. Furthermore, normal AET values have been found in up to 30% of patients with reflux esophagitis [7].

To overcome the limitations of AET, symptom–reflux association indexes have been developed to document a cause–effect relationship between reflux episodes and symptoms [7]. Symptom association probability (SAP) and symptom index (SI), regarded as positive when >95 and >50%, respectively, are the most widely adopted in clinical practice [4]. SAP/SI positivity with normal AET defines the clinical category of hypersensitive esophagus (HE), which has been included within the realm of GERD on the basis of Rome III criteria for esophageal disorders [5].

However, reflux assessment only based on pH criteria has several limitations. In fact, it has been shown that pH drops below 4.0 units may also be due to acidic swallows, which may cause an overestimation of esophageal exposure to gastric contents [8]. Moreover, in vitro studies have shown that the proteolytic activity of pepsins and not hydrochloric acid per se is essential for esophageal mucosa damage to occur [9]. Proteolytic activity of pepsins is maintained up to pH 6.0 units [10], and healing of mucosal breaks occurs through reparative processes that are inhibited at pH < 6.5 units [11]. In vivo studies have shown that PPI therapy transforms acid into weakly acidic refluxes [12], which have been implicated in the pathogenesis of refractory reflux esophagitis [13] and cannot be reliably assessed by pH-only monitoring [4, 8, 12–14].

Combining esophageal bile and acid reflux monitoring does not add any relevant piece of information for GERD diagnosis [14]. It has long been recognized that bile reflux closely tracks with acid reflux and can be suppressed by PPI therapy [14]. Moreover, using the above combination, it has been shown that bile reflux does not differ between PPI-responsive and PPI-refractory GERD patients [15]. Therefore, the interest for bile reflux monitoring has waned [14].

Conventional Assessment of Impedance-pH Monitoring

The combination of pH with impedance monitoring provides a comprehensive characterization of reflux episodes based on both physical (i.e., liquid, gas, or mixed) and chemical properties of the refluxate [16]. Gastroesophageal reflux episodes are detected on the basis of characteristic impedance changes (i.e., distal to proximal progressing changes in intraluminal impedance), and data from the esophageal pH sensor are simply used to distinguish acid (nadir pH < 4) from non-acid, namely weakly acidic (nadir pH 4–7) and weakly alkaline refluxes (nadir pH > 7) [16]. No correlation between bile reflux, as measured with bile reflux monitoring, and non-acid reflux, as measured with impedance-pH monitoring, has been shown [17].

Currently, impedance-pH monitoring is regarded as the gold standard for the assessment of reflux [18]. Pilot studies have shown that assessment of SAP and SI for non-acid reflux events afforded a 16–33% diagnostic gain in patients evaluated on-PPI therapy [19–21]. On the other hand, off-PPI SAP positivity for non-acid refluxes led to a modest 10–12% diagnostic gain [22, 23]. Unfortunately,

patients frequently do not perceive symptoms during a 24-h impedance-pH study and/or admit inaccurate symptom recording, so that SAP and SI represent overly patient-dependent variables. Furthermore, SAP and SI do not measure the severity and clinical impact of symptoms. For instance, nocturnal heartburn and regurgitation may interrupt sleep and are undoubtedly troublesome symptoms, but SAP and SI may nonetheless result negative because they are calculated for the entire 24-h monitoring period. Moreover, SAP and SI positivity is determined by chance when reflux rates are low [24], so that their clinical value is questionable.

In addition to AET and SAP/SI, the number of total (acidic, weakly acidic, and weakly alkaline) reflux events can be reliably assessed at impedance-pH monitoring and represents a parameter scarcely affected by PPI therapy [12]. An abnormal number of reflux events at on-PPI impedance-pH monitoring is predictive of an abnormal AET, as confirmed by off-PPI wireless pH monitoring [25]. In a study performed on-PPI therapy, the assessment of the number of reflux events combined with SAP and SI allowed to diagnose PPI-refractory NERD in two-thirds of cases, as opposed to less than half of cases by assessing SAP/SI only [26]. Objectively documented positive surgical outcome has confirmed the diagnostic specificity of the on-PPI number of reflux events, as combined with SAP/SI positivity for weakly acidic refluxes, in patients with PPI-refractory typical GERD [27–29].

Novel Impedance Parameters

Antegrade and retrograde bolus transit of both liquid and gas [14, 16, 18] can be evaluated by impedance monitoring. In addition to detection of all types of reflux events, impedance monitoring also allows assessment of esophageal clearance of gastroesophageal reflux, which is biphasic, including both volume and chemical clearance [30, 31].

Volume clearance consists of a secondary peristaltic wave, which is elicited by esophageal stretch receptors and removes around 90% of the refluxate, determining the end of a reflux episode [32]. At impedance monitoring, volume clearance can be evaluated with bolus clearance time and percent bolus exposure, but these parameters did not prove to be clinically useful [33].

Chemical clearance consists of a salivary swallow, elicited by an esophago-salivary vagal reflex and delivering salivary bicarbonate and epidermal growth factor to the esophagus, so that distal esophageal pH increases and repair of reflux-induced mucosal damage can occur [11, 30]. After the end of a reflux episode, an impedance drop originating in the upper esophagus and reaching the lower part of the organ signals the peristaltic transit of saliva [34] and has been defined as a post-reflux swallow-induced peristaltic wave (PSPW) [35]. To limit overlap with spontaneous swallowing (64 swallows per hour, approximately 1 per min during the daytime period) [36], only PSPWs occurring within 30 s from the end of reflux episodes (Fig. 1) are considered for calculation of the PSPW index, a new parameter which is obtained dividing the number of refluxes followed within 30 s by a PSPW by the number of total refluxes [35]. The PSPW index has been shown to efficiently separate ERD from NERD patients and both from healthy subjects at off-PPI impedance-pH monitoring, as well as ERD from NERD patients and both from patients with FH at on-PPI impedance-pH monitoring [35]. These results demonstrated that the esophago-salivary reflex can be elicited by acidic and weakly acidic refluxes as well. Accordingly, in patients with PPI-refractory heartburn on-therapy PSPW index was significantly lower in PPI-refractory reflux esophagitis than in healed reflux esophagitis and in NERD, and was the only impedance-pH parameter associated with PPI-refractory mucosal damage [37]. Moreover, at on-PPI impedance-pH monitoring lower values of PSPW index were the only impedance-pH parameter associated with neoplastic progression, i.e., incident dysplasia at 3-year follow-up, in patients with Barrett's esophagus on continuous PPI treatment [38]. These results strongly suggest that impairment of chemical clearance plays a key role in the pathogenesis of reflux-induced esophageal mucosal damage.

Impedance monitoring also allows the measurement of baseline impedance: low values, unaffected by circadian variations [39], reflect reflux-induced impairment of mucosal integrity even in the absence of macroscopic damage [40]. It has been shown that the mean of three 10-minute nighttime periods, selected avoiding reflux episodes, swallows, and pH drops (Fig. 2), accurately reflects the 6-h nocturnal bedtime period, which is less influenced by swallowing activity as opposite to the diurnal one [41]. In endoscopy-negative heartburn patients with normal AET and negative SAP/SI, lower values of mean nocturnal baseline impedance (MNBI) have been found in patients with PPI-responsive heartburn as compared to those with PPI-refractory heartburn [42]. These findings confirm that conventional impedance-pH variables are not accurate enough for separation of GERD from FH.

In a multicenter off-therapy impedance-pH study, the PSPW index and MNBI distinguished 68 ERD and 221 NERD patients from 50 healthy controls with higher diagnostic accuracy than conventional impedance-pH parameters [43]. By means of receiver operating characteristic (ROC) analysis, optimal cutoff values for PSPW index (61%) and MNBI (2292 Ohms) were defined. The area under the curve (AUC) of the PSPW index (0.977) was excellent (>0.9) and significantly greater than that of

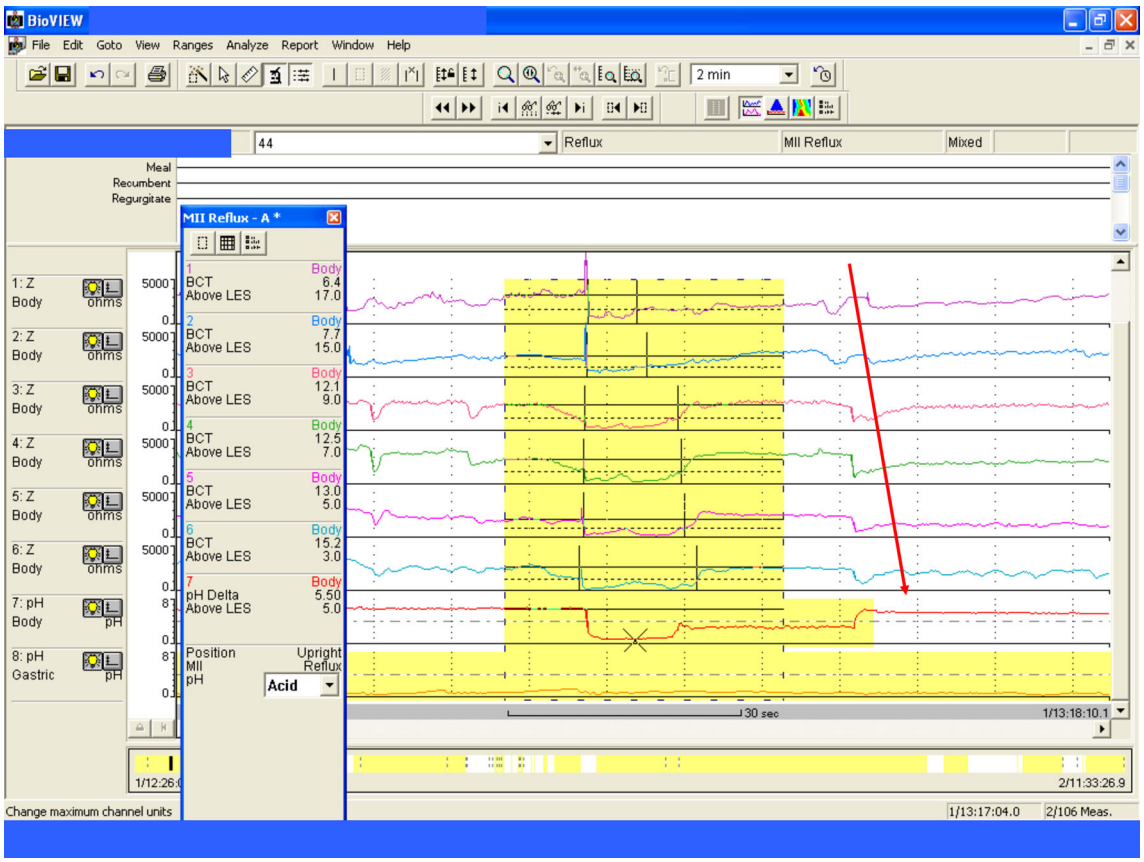

Fig. 1 Post-reflux swallow-induced peristaltic wave (PSPW). Impedance-pH tracing—an acidic reflux episode is followed within 30 s by an impedance drop from the proximal to the distal esophagus (*red arrow*), which represents a post-reflux swallow-induced peristaltic wave (PSPW)

all the other impedance-pH parameters [43]. In NERD cases, PSPW index and MNBI showed a higher sensitivity and better overall diagnostic accuracy in comparison with AET, number of reflux events, and percent bolus exposure. NERD diagnosis was confirmed by conventional pH-only criteria in 75% of cases, and by impedance-pH criteria, including PSPW index and MNBI, in 98% cases ($P = 0.001$) [43]. The results of this study, showing the significant diagnostic gain afforded by PSPW index and MNBI while confirming the pitfalls of conventional impedance-pH parameters (Table 1), were regarded as emphasizing the clinical value of impedance-pH monitoring [33].

Recently, Rome IV criteria for esophageal disorders have defined NERD on the basis of abnormal AET only [44]. HE, defined by positive SAP/SI with normal AET, has been separated from GERD and included within the spectrum of functional esophageal disorders, differently from Rome III criteria [44]. Heartburn relief by PPIs as a criterion for defining GERD has been tempered because of the reportedly high placebo response and limited predictive value [44]. However, it can be argued that the moderate diagnostic sensitivity of AET can have influenced the reportedly [45] moderate diagnostic yield of a PPI trial. The negative results of a diagnostic test in the presence of a definite responsiveness of typical symptoms to a specific therapy should stimulate the search for more efficient diagnostic methods.

After Rome III criteria, both electron [46] and light [47] microscopy studies have shown that microscopic esophagitis is much more frequently detected in patients with HE than in those with FH. In a recent study, PSPW index and MNBI were significantly lower in patients with endoscopy-negative PPI-responsive heartburn as compared to patients with endoscopy-negative PPI-refractory heartburn [48]. At multivariate logistic regression analysis, PSPW index and MNBI were independent predictors of HE, defined as PPI-responsive heartburn with normal AET [48]. At ROC analysis, combined assessment of PSPW index and MNBI allowed excellent separation of HE from FH (AUC 0.957); SAP/SI positivity was found in 62% of HE patients, whereas PSPW index/MNBI positivity was found in 92% of them ($P < 0.0001$) [48]. Therefore, the calculation of PSPW index and MNBI affords diagnosis of HE independently of and significantly better than SAP/SI positivity. Impairment of chemical clearance, as shown by

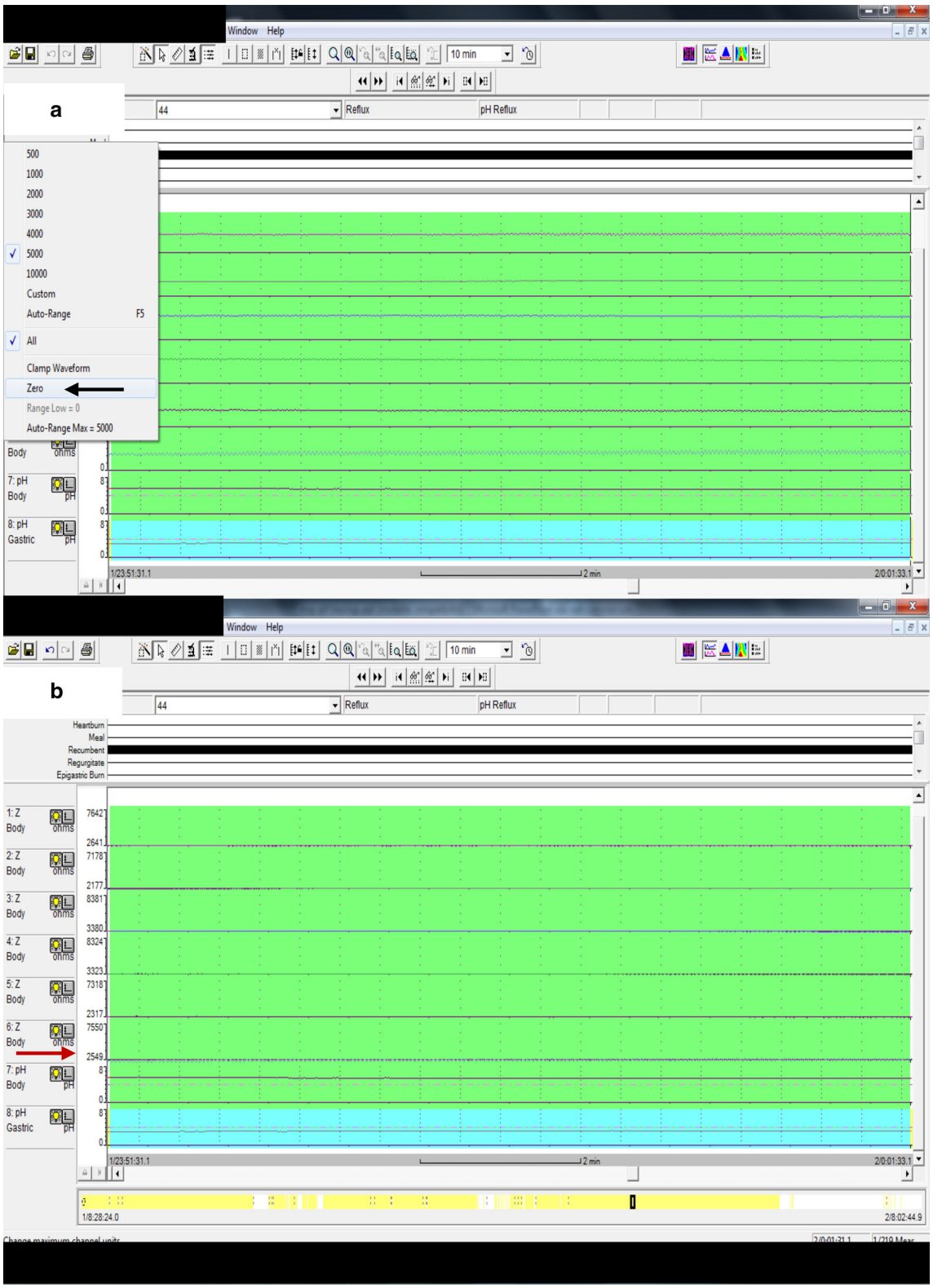

Fig. 2 Mean nocturnal baseline impedance (MNBI). **a** Impedance-pH tracing—a 10-min nighttime recumbent period, avoiding swallows, refluxes, and pH drops, has been selected. The Ohms icon has been clicked with opening of a cascade menu, and then Zero (*black arrow*) is clicked. **b** The baseline impedance values of the selected period are now displayed. The values from the most distal impedance channel (*red arrow*) at three time points (around 1.00, 2.00, and 3.00 am) are summed and the mean calculated to obtain MNBI

Table 1 Pitfalls of conventional of impedance-pH parameters in patients with endoscopy-negative heartburn

	Positivity	Diagnosis	Pitfalls
AET	>3.2–7.2%[a]	NERD	High variability of normative values at different centers
			Day-to-day variability
			Low sensitivity
SAP	>95%	HE	Symptoms may not occur
SI	>50%	HE	Patients frequently admit inaccurate recording
			Positivity is determined by chance when reflux rates are low
			Uncertain significance of discordant results
			Severity and clinical relevance of symptoms are not measured
Reflux events	>48[b]	NERD	Low sensitivity[b]
Percent bolus exposure	>1.9%[b]	NERD	Low sensitivity[b]

Unsatisfactory heartburn response to a PPI trial, normal AET and negative SAP/SI define functional heartburn

AET acid exposure time, *NERD* non-erosive reflux disease, *HE* hypersensitive esophagus, *SAP* symptom association probability, *SI* symptom index

[a] Kahrilas and Quigley [7]

[b] Frazzoni et al. [43]

low PSPW index [48], and loss of mucosal integrity, as documented by low MNBI values [48] and by microscopic esophagitis [46, 47], can explain the increased perception of reflux events and the PPI responsiveness in patients with HE [41–43], suggesting that they really belong to the GERD spectrum and cannot be displaced to the group of patients with esophageal functional disorders.

Recently, Patel et al. [49] showed that low MNBI values, as detected at off-PPI impedance-pH monitoring, represent an independent predictor of GERD response to both medical and surgical treatment. Assessment of MNBI can also be useful at on-PPI impedance-pH monitoring [50]. We found significantly lower values of MNBI and PSPW index in PPI-refractory heartburn patients with persisting reflux esophagitis than in those with healed reflux esophagitis and NERD, and in all these three GERD subgroups than in FH [50]. The comparison of NERD with FH showed high AUCs pertaining to MNBI and PSPW index at ROC analysis (0.677 and 0.886, respectively) [50]. Noteworthy, at multivariate logistic regression analysis the PSPW index was an independent predictor of PPI-refractory GERD as confirmed by the positive surgical outcome, defined by normal conventional impedance-pH findings at 3-year follow-up [50].

How to Monitor Reflux: Off- or On-PPI Therapy?

Impedance-pH monitoring has been recommended in patients with PPI-refractory reflux symptoms and before anti-reflux endoscopic or surgical interventions [3, 14, 51, 52]; moreover, considering the current concerns about PPI safety [53], objective GERD diagnosis may be required in patients with PPI-dependent heartburn to justify long-term PPI need and prescription.

GERD diagnosis may be missed if based only on the analysis of conventional impedance-pH variables, and it has been recognized that the PSPW index and MNBI may enhance the diagnostic yield of impedance-pH monitoring [33, 54]. Heartburn is a highly specific GERD symptom [1–3], and PSPW index and MNBI have shown high diagnostic accuracy both on- and off-PPI therapy. Impedance-pH monitoring should be performed on-PPI therapy when the clinical questions are to distinguish between reflux-related and reflux-unrelated PPI-refractory heartburn and to find the reasons for PPI refractoriness, e.g., poor compliance, inadequate acid suppression, or high burden of weakly acidic refluxes. On the other hand, when GERD diagnosis is still in doubt, but must be firmly confirmed, e.g., before anti-reflux endoscopic or surgical interventions, impedance-pH testing should be performed after two-week PPI washout (Fig. 3).

PSPW Index and MNBI: Ready for Prime Time?

We have shown high diagnostic accuracy, reproducibility, and applicability of PSPW index and MNBI [35, 41–43, 48, 50]. Calculation is easy to perform, and cutoff normative values have been established with ROC analysis [43] (Table 2). Of note, several studies from other groups have emphasized the clinical value of intraluminal baseline impedance [39, 40, 49, 55, 56] and of chemical clearance [34, 57] assessment.

Concerns have been raised about the necessity of a manual review of the entire impedance-pH study to calculate the PSPW index [33]. However, careful manual review of impedance-pH tracings is routinely warranted to calculate conventional variables, because automatic

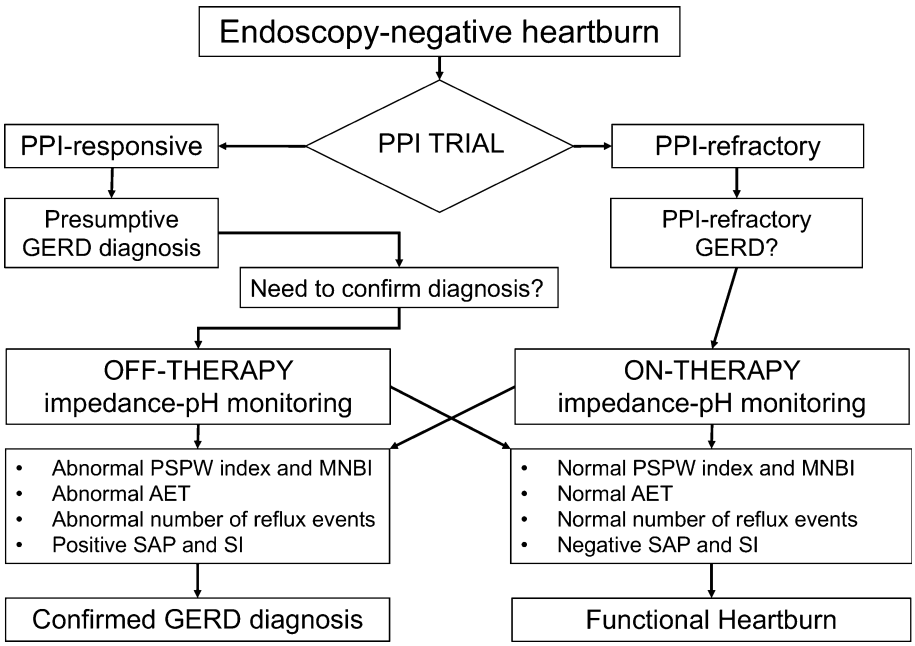

Fig. 3 Algorithm for GERD diagnosis in endoscopy-negative heartburn. Positive response to a PPI trial (standard or high dosage, up to 8 weeks) is sufficient for a presumptive GERD diagnosis. Heartburn refractory to 8-week high-dosage PPI dictates on-therapy impedance-pH monitoring to clarify the mechanism(s) of PPI refractoriness and distinguish reflux-related from reflux-unrelated PPI-refractory heartburn. Impedance-pH monitoring must always be preceded by esophageal manometry. Before anti-reflux surgical or endoscopic interventions, doubtful diagnoses must be confirmed by off-therapy impedance-pH testing after two-week PPI withdrawal. *PPI* proton pump inhibitor, *GERD* gastroesophageal reflux disease, *PSPW* post-reflux swallow-induced peristaltic wave, *MNBI* mean nocturnal baseline impedance, *AET* acid exposure time, *SAP* symptom association probability, *SI* symptom index

Table 2 Assessment, calculation, and normal values of PSPW index and MNBI at impedance-pH monitoring

	Assessment	Calculation	Normal values
PSPW index	Reflux events followed by a PSPW within 30 s are summed by means of a digital counter, while the number of total refluxes is automatically provided by the software at the end of the manual review	Number of total refluxes followed by a PSPW within 30 s divided by the number of total refluxes	>61%[a]
MNBI	Selection of three 10-min nighttime recumbent periods with avoidance of reflux events, pH drops and swallows	Baseline impedance values in the three periods are summed, and the mean is calculated	>2292 Ohms[a]

PSPW post-reflux swallow-induced peristaltic wave, *MNBI* mean nocturnal baseline impedance

[a] Frazzoni et al. [43]

software analysis is hindered by a considerable error rate and does not guarantee accurate results [58–60].

Calculation of PSPW index and MNBI requires a few minutes during the manual analysis of tracings [35, 41]. It is important to underline that any extra-time required for calculation of PSPW index and MNBI is justified when the clinical issue is a reliable diagnosis of GERD, especially when patients are candidate for anti-reflux surgical or endoscopic interventions. Further, we are quite confident that future releases of software analysis will incorporate automatic methods to assess these parameters, as occurred in the past with symptom–reflux association analysis.

In our opinion, PSPW index and MNBI are ready for prime time and should be routinely assessed in patients with endoscopy-negative heartburn evaluated with impedance-pH monitoring. Whether PSPW index and MNBI can improve the diagnostic yield of impedance-pH monitoring also in patients with non-cardiac chest pain and extra-esophageal symptoms suspected to be due to GERD is an open issue to be assessed in future studies.

Conclusions

Impedance-pH monitoring provides the most comprehensive assessment of gastroesophageal reflux. The diagnostic sensitivity and reliability of conventional impedance-pH variables, namely AET, SAP, SI, number of reflux events,

and percent bolus exposure, is suboptimal. PSPW index and MNBI are objective and reliable parameters, which significantly and consistently increase the diagnostic yield of impedance-pH monitoring, both off- and on-PPI therapy, in patients with PPI-responsive and PPI-refractory heartburn. We propose that analyses of the PSPW index and MNBI become part of the standard assessment of impedance-pH tracings for GERD diagnosis in patients with endoscopy-negative heartburn.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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