

Critical appraisal of Rome IV criteria: hypersensitive esophagus does belong to gastroesophageal reflux disease spectrum

Leonardo Frazzoni^a, Marzio Frazzoni^b, Nicola de Bortoli^c, Salvatore Tolone^d, Irene Martinucci^c, Lorenzo Fuccio^a, Vincenzo Savarino^e, Edoardo Savarino^f

University of Bologna; Baggiovara Hospital, Modena; University of Pisa; 2nd University of Napoli; University of Genova; University of Padova, Italy

Abstract

The Rome IV Committee introduced a major change in the classification of functional gastrointestinal disorders, proposing a more restrictive definition of gastroesophageal reflux disease (GERD). It was suggested that hypersensitive esophagus (HE) may sit more firmly within the functional realm. It was suggested that GERD diagnosis should be based upon abnormal acid exposure time (AET) only, implying no advantage of impedance-pH over pH monitoring. Symptom association probability (SAP), symptom index (SI) and heartburn relief with proton pump inhibitor (PPI) therapy were regarded as unreliable, whereas a lack of response to PPI was considered as evidence of functional heartburn. These assumptions are contradicted by numerous studies showing the clinical relevance of weakly acidic refluxes and the diagnostic utility of SAP, SI and new impedance parameters, namely the post-reflux swallow-induced peristaltic wave (PSPW) index and the mean nocturnal baseline impedance (MNBI). The PSPW index and MNBI provide significant diagnostic advantage, particularly in patients with normal AET who can be classified as HE when both parameters are abnormal, even though SAP and SI are negative. Visceral pain modulators are recommended by the Rome IV Committee despite scanty evidence of efficacy, but a positive outcome with medical or surgical anti-reflux treatment has been reported by several studies of HE patients. Therefore, we believe that patients with endoscopy-negative heartburn should be investigated by means of impedance-pH monitoring with analysis of PSPW index and MNBI: such an approach provides accurate identification of HE cases, who remain, in our opinion, within the realm of GERD and should be treated accordingly.

Keywords Gastroesophageal reflux disease, impedance-pH monitoring, proton pump inhibitor-refractory GERD, baseline impedance, post-reflux swallow-induced peristaltic wave index

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^aDepartment of Medical and Surgical Sciences, University of Bologna (Leonardo Frazzoni, Lorenzo Fuccio); ^bDigestive Pathophysiology Unit, Baggiovara Hospital, Modena (Marzio Frazzoni); ^cDepartment of Translational Research and New Technology in Medicine and Surgery, University of Pisa (Nicola de Bortoli, Irene Martinucci); ^dGeneral and Bariatric Surgery Unit, Department of Surgery, 2nd University of Napoli (Salvatore Tolone); ^eGastroenterology Unit, Department of Internal Medicine, University of Genova (Vincenzo Savarino); ^fGastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padova (Edoardo Savarino), Italy

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Correspondence to: Dr. Marzio Frazzoni, Fisiopatologia Digestiva, AOU Modena, Ospedale Baggiovara, Viale Giardini 1355, 41100 Modena, Italy, e-mail marziofrazzoni@gmail.com

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Introduction

Gastroesophageal reflux disease (GERD) is characterized by troublesome symptoms or mucosal lesions due to reflux of gastric contents into the esophagus. The typical GERD syndrome is characterized by heartburn and regurgitation, and proton pump inhibitor (PPI) therapy represents the mainstay of medical treatment for typical GERD, with very high efficacy in heartburn relief and healing of erosive reflux disease (ERD) [1-3]. Non-ERD (NERD) has been defined by endoscopy-negative heartburn (ENH) and evidence of a direct link of the symptom with reflux, as shown by pH or impedance-pH monitoring and/or response to anti-reflux therapy [4]. Since endoscopy shows reflux esophagitis in less than one third of patients with heartburn, symptom remission with a PPI trial has been considered sufficient to confirm a diagnosis of GERD [1-3].

The Rome Committees began in the mid 1980s as a series of meetings that developed consensus criteria for research purposes and care of patients with functional gastrointestinal disorders [5]. Functional heartburn (FH) has been one of the most debated conditions addressed by the Rome experts [6-8]. According to the Rome II criteria [6], patients with ENH were classified as FH or NERD on the basis of normal or pathologic acid exposure time (AET), as detected by traditional ambulatory esophageal pH monitoring. The definition of GERD was expanded in the Rome III criteria [7] to include patients with hypersensitive esophagus (HE), defined as satisfactory evidence of a relationship between heartburn and acid reflux events, based either on a pH study or on symptom relief from a PPI trial. More recently, the Rome IV Committee proposed that HE be separated from GERD, with this subgroup of patients being classified within the realm of functional esophageal disorders along with, but separate from FH [8].

GERD diagnosis: the real challenge

A gold standard for GERD diagnosis has not yet been widely recognized [1-4]. Since in the vast majority of patients with reflux symptoms visible mucosal lesions are not detected on upper gastrointestinal endoscopy, reflux monitoring is required to objectively document GERD in the vast majority of cases [1-4]. By means of pH monitoring, the total percentage of time with pH <4.0, namely the acid exposure time (AET), can be assessed and when abnormal values are found GERD is confirmed [4]. However, the limitations of AET have long been documented, consisting in high variability of normative values and false negative results in up to 30% of patients with reflux esophagitis [9,10]. To overcome these limitations, symptom/reflux association indexes, namely symptom index (SI) and symptom-association probability (SAP), were developed to document a cause-and-effect relationship between acid reflux episodes and symptoms in endoscopy-negative, pH-negative heartburn cases [9]. The diagnostic category of HE [7] or reflux hypersensitivity [8] has been proposed in order to better identify pH-negative cases with positive SI or SAP.

In recent years, *in vitro* studies have shown that the proteolytic activity of pepsins is necessary for reflux-induced esophageal mucosa damage to occur, and such activity is maintained up to pH 6.0 units [11]. Moreover, it has been observed that healing of mucosal breaks occurs through reparative processes that are inhibited at pH <6.5 units [12]. Refluxes with pH >4.0 units can be reliably assessed with combined impedance-pH monitoring, which detects all reflux episodes by impedance changes and has been regarded as the gold standard for a comprehensive assessment of reflux [13,14]. With the advent of impedance-pH monitoring, SAP and SI have been used to demonstrate a direct link between non-acid reflux episodes and symptoms and to increase our ability to diagnose GERD, showing a higher diagnostic gain on PPI therapy [15-18]. Electron [19] and light [20] microscopy studies have shown that microscopic esophagitis is much more frequently detected in patients with HE, as defined by SAP/SI positivity, than in FH cases. However, the major problem with symptom/reflux association indexes

is that they are overly patient-dependent: patients often do not perceive symptoms during the impedance-pH study or admit inaccurate symptom recording. Furthermore, SAP/SI positivity is reportedly determined by chance when reflux rates are low [21]. Impedance monitoring also allows assessment of the total number of reflux events, independently of pH. The total number of reflux events is scarcely affected by PPI therapy [22] and abnormal values at on-PPI testing can predict abnormal AET at off-therapy evaluation [23]. By using on-PPI impedance-pH monitoring, it has been shown that weakly acidic refluxes represent the vast majority of reflux events and of symptom-associated refluxes in patients with PPI-refractory typical GERD [24]: notably, in parallel with complete symptom relief, they are nearly abolished by successful laparoscopic fundoplication [25-27], and the results of these studies represent direct *in vivo* evidence that weakly acidic refluxes have a key role in the pathogenesis of PPI refractoriness.

Assessment of AET, SAP, SI and number of reflux events represents the traditional approach to analysis of impedance-pH tracings, quite similar to that of pH monitoring. In recent years, innovative approaches have been proposed. Baseline impedance can be accurately measured in impedance tracings and low values reflect reflux-induced impairment of mucosal integrity, even in the absence of macroscopic damage [28] and without circadian variations [29]. It has been shown that the mean of three 10-min nighttime periods, selected to avoid refluxes, swallows and pH drops, accurately reflects the 6-h nocturnal bedtime period [30]. Interestingly, similar lower values of nocturnal baseline impedance have been found in SAP/SI positive and SAP/SI negative patients with PPI-responsive heartburn as opposed to SAP/SI negative patients with PPI-refractory heartburn and normal AET [31], suggesting that SAP/SI positivity does not accurately distinguish HE from FH. In addition to detection of all types of reflux events, impedance monitoring also allows the assessment of clearance of refluxate. Volume clearance consists of a secondary peristaltic wave, elicited by esophageal stretch receptors and removes around 90% of the refluxate, determining the end of a reflux episode [32]. Chemical clearance consists of a salivary swallow, elicited by a post-reflux esophago-salivary vagal reflex [33] and delivering salivary bicarbonate and epidermal growth factor to the esophagus, thus augmenting pH and hastening repair of reflux-induced mucosal damage. An impedance drop originating in the upper esophagus and reaching the lower part of the organ signals the peristaltic transit of saliva and has been defined as a post-reflux swallow-induced peristaltic wave (PSPW). An index of chemical clearance, namely the PSPW index, can be obtained by dividing the number of refluxes followed by a PSPW within 30 sec by the number of total refluxes [34]. In a pilot single-center study, lower values of PSPW index at off-PPI impedance-pH testing were found in ERD as compared to NERD cases and in both GERD subgroups as opposed to healthy controls; similar results were observed at on-PPI testing comparing PPI-refractory ERD and NERD patients and both with FH cases [34].

In a multicenter off-PPI impedance-pH study, the PSPW index and MNBI distinguished 221 NERD patients from 50 healthy controls better than AET; a significant direct

correlation between the two parameters was found and an excellent area under the curve (AUC) of the PSPW index at receiver operating characteristic (ROC) analysis (0.977) was observed [35]. NERD was defined on the basis of a 6-month history of recurrent troublesome heartburn, repeatedly abolished by PPI courses. Notably, only 118 of 221 (53%) NERD cases were pH-positive (abnormal AET), while in the 103 pH-negative NERD cases (normal AET) the diagnostic accuracy of PSPW index and MNBI was 86% and 67% in the 65 SAP/SI positive cases and 82% and 76% in the 38 SAP/SI negative cases, respectively. NERD diagnosis was confirmed by conventional pH-only criteria, namely AET and SAP/SI positivity for acid refluxes, in 75% of cases only, and by impedance-pH criteria, including PSPW index and MNBI, in 98% of cases ($P=0.001$) [35].

In a subsequent off-PPI impedance-pH study, 125 pH-positive and 108 pH-negative PPI-responsive NERD patients were compared to 70 FH patients, defined by ENH totally refractory to 8-week high-dose PPI therapy with normal AET and negative SAP/SI [36]. PSPW index and MNBI were significantly lower in pH-positive than in pH-negative NERD cases, and in both groups compared to FH cases. By multivariate logistic regression analysis, PSPW index and MNBI were found to be independent predictors of HE, defined by normal AET and definitely PPI-responsive heartburn, i.e., heartburn repeatedly responsive to PPI courses and quickly recurring after PPI withdrawal [36]. SAP/SI positivity was found in 62% of HE patients, whereas PSPW index/MNBI positivity was found in 92% of them, affording a significant ($P<0.0001$) diagnostic gain in one third of cases [36]. The combined assessment of PSPW index and MNBI provided excellent separation of HE from FH on ROC analysis (AUC 0.957) [36].

Moreover, PSPW index and MNBI have been proved useful at on-PPI impedance-pH testing [37]. In a multicenter study conducted in 189 patients with PPI-refractory heartburn, i.e., troublesome heartburn persisting despite 8-week high-dose PPI therapy, significantly lower values of PSPW index and MNBI were found in patients with persisting reflux esophagitis than in those with healed reflux esophagitis and NERD, and in all these three GERD subgroups than in cases with FH [37]. On ROC analysis, comparing NERD with FH, the AUC of PSPW index and MNBI was 0.886 and 0.677, respectively [37]. Notably, in multivariate logistic regression analysis the PSPW index was an independent predictor of PPI-refractory GERD, confirmed by objectively documented 3-year positive surgical outcome [37]. Interestingly, Patel *et al* showed that low MNBI values, measured at off-PPI impedance-pH monitoring in accordance with the method proposed by Martinucci *et al* [30], represent an independent predictor of GERD response to medical as well as surgical anti-reflux treatment [38].

Furthermore, in a very recent multicenter off-therapy impedance-pH study, 317 patients with PPI-responsive were compared to 108 patients with PPI-refractory heartburn [39]. On multivariate logistic regression analysis, AET, MNBI, and PSPW index were the only factors independently associated with PPI responsiveness [39]. On ROC analysis, PSPW index (AUC 0.794) and MNBI (AUC 0.742), both separately and

combined (AUC 0.811), were more efficient predictors of PPI-responsiveness than AET (AUC 0.687) [39], overcoming its well documented day-to-day variability [40].

Taken together, the results of the studies evaluating MNBI and PSPW index [30,31,34-39] show that these novel impedance parameters provide a significant diagnostic yield compared with conventional AET, SAP, SI, and number of reflux events, and should be routinely adopted for both research and clinical purposes. Low values of PSPW index reflect impairment of chemical clearance, with consequent stasis of toxic refluxate within the esophagus and loss of mucosal integrity, documented by the directly related low values of MNBI: these mechanisms can explain the increased perception of reflux events and the PPI responsiveness in patients with HE, suggesting that they really belong to the GERD spectrum and cannot be displaced to the realm of functional gastrointestinal disorders.

The pitfalls of Rome IV

The major problem with the Rome IV criteria is that only acid exposure was considered in the interplay between heartburn and GERD [8]. Accordingly, NERD was defined on the basis of abnormal AET only, whereas HE, characterized by positive SAP/SI and normal AET, was considered as separate from GERD (in contrast to Rome III [7]) and was included within the spectrum of functional esophageal disorders [8]. Justification for the criteria change are that “although patients with symptom/reflux correlation to physiologic reflux events may respond to PPI therapy, the most logical pathophysiologic explanation is consistent with the current understanding of visceral hypersensitivity and mechanisms of peripheral or central sensitization.” On the other hand, the Rome IV Committee stated that “lack of response to PPI therapy should be considered as an important diagnostic criterion to establish that symptoms are not related to gastroesophageal reflux. Clinical experience suggests that a lack of response to PPI probably has a high negative predictive value for the diagnosis of GERD”. However, evidence-based medicine does not rely on logical concepts or clinical experience.

Indeed, the concept of visceral hypersensitivity as the dominant mechanism of HE is contradicted by many studies. Patients with FH overlap with functional dyspepsia [41] and irritable bowel syndrome [42] significantly more often than those with HE and NERD. The Rome IV Committee admitted that only one study supports the efficacy of visceral pain modulators in HE [43], but omitted to report a more recent randomized placebo-controlled trial in which imipramine and placebo were similarly ineffective in HE and in FH [44]. On the other hand, positive outcomes with medical or surgical anti-reflux treatment have been consistently reported in HE [25-27,38,39,45-50] and two recent consensus recommend laparoscopic fundoplication as the treatment of choice in well-documented PPI-refractory GERD [51,52].

In contrast with Rome IV, the Montreal Global Consensus [1] and current AGA and ACG Guidelines [2,3] stated that relief of heartburn, the cardinal GERD symptom,

with PPI therapy confirms the diagnosis of GERD. Heartburn suppression by PPIs as a diagnostic criterion for GERD in patients with ENH has been criticized by Rome IV because of the high placebo response and its limited predictive value [8]. However, the placebo response rate was less than 15% in studies of PPI therapy in patients with heartburn [53], and the response rates in ERD and NERD are similar when the NERD diagnosis is objectively documented on the basis of direct reflux testing, including abnormal AET or positive SAP/SI [54]. Furthermore, the moderate diagnostic sensitivity of AET and SAP could have influenced the reportedly moderate diagnostic specificity of a PPI trial [55]. When a diagnostic test provides negative results, despite definite responsiveness of typical symptoms to a specific therapy, more efficient diagnostic methods need to be sought. In our studies that aimed to assess the diagnostic yield of PSPW index and MNBI [35,36,39], we defined GERD in ENH patients when rapid symptom relief was achieved with PPI therapy, heartburn recurred early after PPI withdrawal, and prompt symptom suppression with repeated PPI therapy was again reported: this criterion cannot be considered simply a positive response to a PPI trial, but represents a definite PPI responsiveness. In our studies, PSPW index and MNBI were abnormal in the vast majority of definitely PPI-responsive heartburn cases with normal AET and negative SAP/SI [35,36] and predicted PPI responsiveness better than AET [39]. Moreover, we have shown the pathophysiologic consistency of PSPW index and MNBI in patients with PPI-refractory heartburn by the detection of progressively lower values in NERD, healed reflux esophagitis and persistent reflux esophagitis, and significantly lower values in all these three GERD subgroups than in FH cases [37]. Therefore, considering the high diagnostic yield afforded by PSPW index and MNBI, we believe that analyses of these impedance parameters should become part of the diagnostic algorithm in patients with ENH [56]. Symptom/reflux association indexes and number of reflux events should not be abandoned, however, owing to their usefulness as predictors of a favorable outcome with medical or surgical therapy [25-27,45-50]. When AET is normal, concordant SAP/SI positivity and/or concordant abnormality of PSPW index and MNBI and/or abnormal number of reflux events document pH-negative NERD, i.e., HE, which belongs to the realm of GERD and should be managed accordingly.

The Rome IV Committee suggests that HE diagnosis requires exclusion of eosinophilic esophagitis (EoE) and major motor disorders (achalasia, esophago-gastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis), implying that multiple esophageal biopsies and high-resolution manometry are routinely warranted [8]. However, heartburn and chest pain in adults with EoE are not dominant or co-dominant symptoms and when present accompany dysphagia [57]; moreover, in the absence of solid food dysphagia and food impaction, high intraepithelial eosinophil counts are not specific for EoE [58] and routine esophageal biopsies are not recommended [59,60]. Esophageal manometry is routinely warranted before pH or impedance-pH monitoring, for correct placement of the pH or impedance-pH catheter and for exclusion of achalasia and other major

esophageal motility disorders, but it should be considered that both aims can be accomplished by high-resolution as well as by conventional manometry [61,62].

Summing up, neither the relevance of weakly acidic reflux in the pathogenesis of PPI-refractory GERD nor the insufficient diagnostic accuracy of conventional pH monitoring were adequately considered by the Rome IV Committee. In the classification scheme proposed by Rome IV, patients with PPI-refractory ENH and proven GERD should be further classified on the basis of the results of on-PPI impedance-pH testing. Indeed, on-PPI impedance-pH monitoring is regarded as the test of choice to investigate the mechanisms of PPI-refractory heartburn, i.e., poor compliance, inadequate acid suppression, high burden of weakly acidic refluxes or reflux-unrelated, namely FH [63], but cannot be based on AET alone, which has long been recognized as scarcely useful in the clinical setting of PPI refractoriness during ongoing PPI therapy [64]. The analysis of on-PPI impedance-pH tracings based on AET and SAP/SI only in patients with proven GERD would inevitably result in a reclassification of the majority of these cases as FH, thus contradicting the previous off-PPI diagnosis of GERD. As far as unproven GERD in the Rome IV classification scheme is concerned, there is vast evidence that off-PPI pH monitoring cannot afford an accurate enough diagnosis of GERD and that impedance-pH monitoring represents the test of choice [4,17,18,35,36,39].

GERD is a spectrum disease, ranging from NERD to ERD and Barrett's esophagus [4,65]. HE represents a particular NERD subgroup, distinguished from FH by impairment of chemical clearance and mucosal integrity [30,31,35,36,39], which explain the frequently positive response to medical and surgical anti-reflux treatment [25-27,35-37,39,45-50]. Thus, we propose an evidence-based classification scheme of ENH, relying on impedance-pH monitoring with analysis of conventional and novel impedance-pH parameters (Fig. 1), with the cutoff values reported in Table 1 [35]. When AET is normal, concomitant abnormality of PSPW index and MNBI

Table 1 Cutoff values for impedance-pH parameters*

Parameter	Positivity
AET	>3.2%
Total refluxes	>48
SAP	>95%
SI	>50%
PSPW index	<61%
MNBI	<2292 Ω

*Established with ROC analysis comparing 50 healthy subjects with 289 GERD patients [35]. The PSPW index is calculated by dividing the number of total refluxes followed by a PSPW within 30 sec by the number of total refluxes. The MNBI is assessed from the most distal impedance channel by selecting three 10-min nighttime recumbent periods with avoidance of reflux events, pH drops and swallows; the mean of the 3 measurements is then calculated manually

ROC, receiver operating characteristic; GERD, gastroesophageal reflux disease; AET, acid exposure time; SAP, symptom association probability; SI, symptom index; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance

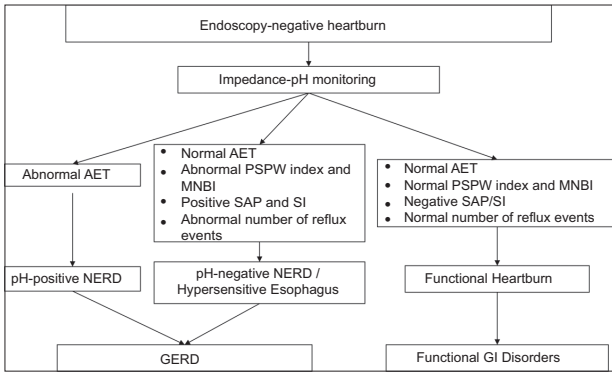


Figure 1 Classification of endoscopy-negative heartburn
 The Figure suggests a classification scheme and does not represent a diagnostic algorithm
 AET, acid exposure time; MNBI, mean nocturnal baseline impedance; NERD, non-erosive reflux disease; PSPW, post-reflux swallow-induced peristaltic wave; SAP, symptom association probability; SI, symptom index; GERD, gastroesophageal reflux disease; GI, gastrointestinal

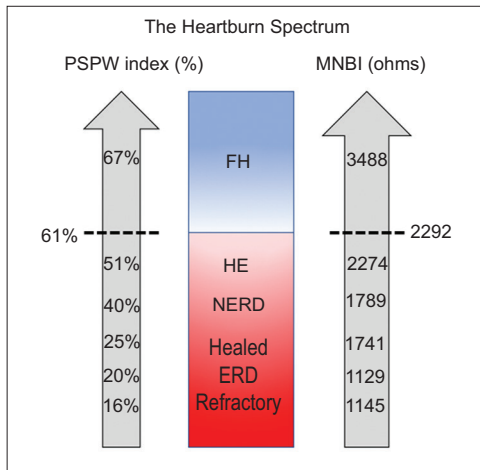


Figure 2 Median and cutoff values of PSPW index and MNBI for the various diagnostic categories in the heartburn spectrum
 Dotted lines indicate cutoff values
 ERD, erosive reflux disease; FH, functional heartburn; HE, hypersensitive esophagus; MNBI, mean nocturnal baseline impedance; NERD, non-erosive reflux disease; PSPW, post-reflux swallow-induced peristaltic wave

establishes HE independently from SAP/SI or number of reflux events. Median values of PSPW index and MNBI for the various diagnostic categories in the heartburn spectrum are shown in Fig. 2.

Concluding remarks

HE is a category that arose from the diagnostic limitations of AET, assessed with traditional pH monitoring, to give a pathophysiological label to endoscopy-negative, pH-negative heartburn. ENH patients should be classified on the basis

of impedance-pH monitoring, the only method affording a comprehensive and accurate assessment of reflux. Many studies have documented that weakly acidic refluxes, which cannot be reliably measured by pH monitoring, play a key role in the pathogenesis of PPI-refractory reflux esophagitis and PPI-refractory ENH, and that HE, i.e., pH-negative heartburn, responds to anti-reflux medical and surgical treatment. PSPW index and MNBI significantly increase the diagnostic yield of impedance-pH monitoring, as performed off- or on-PPI therapy. In our opinion, there is ample evidence that patients with HE should be considered within the GERD spectrum and treated accordingly.

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