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The principles of impedance were first applied to the gastrointestinal tract in 1991. MII testing was approved by the US Food and Drug Administration for esophageal functional testing in 2002. Impedance measures change in resistance (Ohms) of alternating electrical current passing through pairs of metal rings on a catheter. In the empty esophagus, baseline current is conducted between the rings by ions on the mucosa. Because impedance catheters have multiple sets of impedance-measuring rings, bolus movement and direction (antegrade or retrograde) can be assessed [1].

MII-pH monitoring is performed using a polyvinyl catheter (diameter 2.3 mm) equipped with an antimony pH electrode and several cylindrical electrodes, with a length of 4 mm, placed at intervals of about 2 cm to measure the electrical impedance of the esophageal contents at multiple levels along the longitudinal axis of the esophagus [2]. Each pair of adjacent electrodes represents an impedance-measuring segment corresponding to one recording channel. The catheter is positioned with the pH electrode 5 cm above the LES and the six impedance recording channels at 3, 5, 7, 9, 15, and 17 cm above the manometrically defined lower esophageal sphincter (LES). The overall recording time lasts 24 h.

MII-pH provides a detailed characterization of each reflux event including chemical (acid and non-acid reflux) and physical properties (liquid, mixed, gas) [3]

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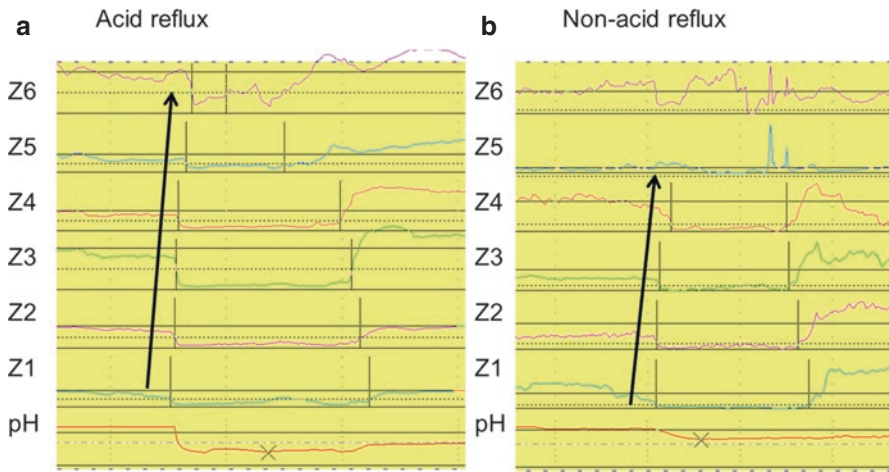
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**Fig. 14.1** Example of two different reflux events: (a) acid reflux event that involves both distal and proximal channels with a contemporary drop of esophageal pH below 4; (b) non-acid reflux event that involves distal channels only, the pH does not drop below 4. Z1-Z6 impedance detection channels

(Fig. 14.1). To date, nonacid reflux represents the majority of reflux episodes in patients with gastroesophageal reflux disease (GERD) on proton pump inhibitor (PPI) therapy [4, 5]. Indeed, the total number of reflux episodes is not affected by the acid-suppressive therapy, and weakly acidic refluxes account for approximately 90% of all reflux episodes on PPI thus representing a potential mechanism underlying failure of PPI treatment in patients with reflux-related symptoms [6, 7]. Moreover, MII-pH monitoring, as well as pH-metry alone, provides the opportunity to assess the temporal relationship between the occurrence of refluxes and the onset of symptoms [8, 9]. The relationship between symptoms and reflux events can be evaluated with symptom index (SI) and symptom association probability (SAP) that are the most commonly employed symptom indices being used [9].

Based on esophageal pH monitoring, NERD patients with a physiological esophageal acid exposure time (AET) and a close temporal relationship between symptoms and reflux events have been defined as hypersensitive to acid stimuli. On the other hand, in line with Rome III criteria, patients with heartburn, normal upper endoscopy, physiological AET, negative correspondence between symptoms and refluxes, and who fail to respond to PPIs are defined as functional heartburn (FH) [10–12]. In this regard, the advent of MII-pH monitoring improved the diagnostic yield of GERD patients mainly by identifying a positive SAP or SI with weakly acidic or weakly-alkaline refluxes [13–19] both in PPI-responsive and in PPI-refractory patients [20, 21]. Indeed, pH-only monitoring and response to PPI therapy underestimate GERD when with MII-pH criteria [20, 22, 23].

On the other hand, all available diagnostic tests for GERD have some limitations. MII-pH drawbacks are mainly due to the day-to-day variability of the test [24–26]. Additionally, the reflux-symptom correlation in patients with GERD who do not

respond to PPI therapy is actually calculated with SI or SAP also if their validity is still uncertain [27, 28]. Recently Zerbib et al. [29] described that MII-pH findings are not always able to predict response to PPIs in patients with reflux-related typical symptoms when the test is performed off-PPI therapy.

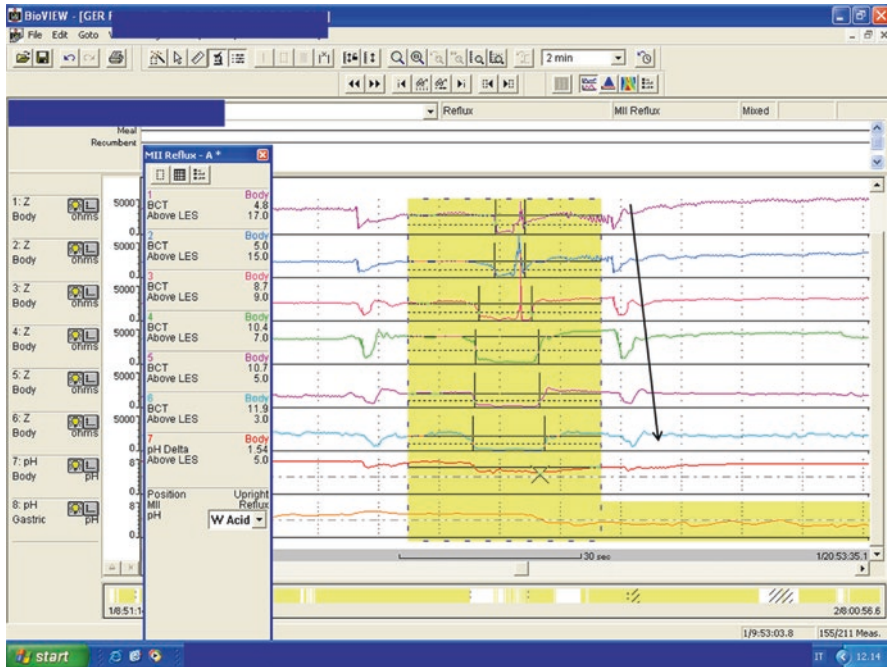
Regarding the clinical utility of pathophysiological investigations in patients with heartburn, we described a group of patients (more than 19% of the whole population enrolled) with heartburn totally suppressed by PPI therapy, in which GERD was not diagnosed with conventional MII-pH criteria [30]. These data suggest that PPI response alone should not always be considered sufficient for GERD diagnosis [30]. Notably, patients with non-erosive reflux disease (NERD) are pathophysiologically heterogeneous and should be accurately studied by means of MII-pH to define the best therapeutic approach [31]. Indeed, a meta-analysis showed that reportedly low response rate in NERD is likely the result of inclusion within this umbrella term of patients with reflux-unrelated heartburn [32].

Recently, the ability of MII-pH testing to better understand GERD's pathophysiology has been improved through the introduction of up-and-coming parameters such as the post-reflux swallow-induced peristaltic wave (PSPW) index, which stand for the efficacy of esophageal chemical clearance [33], and the nocturnal baseline impedance values (MNBI), which indicates impairment of esophageal mucosa integrity [34].

Frazzoni [33], firstly, defined PSPW as an antegrade 50% drop in impedance relative to the pre-swallow baseline originating in the most proximal impedance sites, reaching all the distal impedance sites, and followed by at least 50% return to the baseline in all the distal impedance sites (bolus exit) (Fig. 14.1) [35]. Post-reflux swallows not reaching the distal impedance sites and/or not followed by return to the baseline were excluded. To limit overlap with spontaneous swallowing (64 swallows  $\text{h}^{-1}$ , approximately 1  $\text{min}^{-1}$ ) [36] and considering the latency period of salivary gland response to esophageal acidification (10–15 s) [37], only PSPWs occurring within 30 s from the end of reflux episodes were taken into account (Fig. 14.2).

Impairment of esophageal chemical clearance could represent specific mechanism involved in GERD pathophysiology. PSPW index has been showed to be significantly lower in patients with reflux esophagitis and NERD than in healthy controls or in patients functional heartburn (FH), i.e., with reflux-unrelated heartburn. Moreover, this parameter is not altered after medical or surgical therapy [33]. Moreover, Frazzoni et al. [38] showed that patients with PPI-refractory heartburn/regurgitation and refractory reflux esophagitis were associated with a more severe impairment of chemical clearance but similar levels of acid exposure when compared with those patients with healed reflux esophagitis. Adequate acid suppression was found in the majority of patients with refractory reflux esophagitis who did not record any benefit from further PPI escalation [38]. These data confirmed that both contact time of esophageal mucosa with acidic/weakly acidic refluxate and impairment of chemical clearance (PSPW index) play a relevant role in the pathogenesis of refractory reflux esophagitis.

Frazzoni et al. [39] also evaluated the PSPW index in patients with short-segment Barrett's esophagus with or without mucosal dysplasia. They observed that the



**Fig. 14.2** Impedance-pH tracing showing a weakly acidic reflux followed by a swallow-induced peristaltic wave (*arrow*)

PSPW index was significantly lower in patients with than in patients without dysplasia at the time of surveillance (15 %, vs. 32 %;  $p=0.001$ ) and at the time of diagnosis too. Statistical analysis showed that a PSPW index  $<26\%$  was predictive of incident dysplasia with a 75 % accuracy.

First of all, Farrè and coworkers [34] tested for the first time the hypothesis that multichannel intraluminal impedance (MII) might be a suitable tool for the assessment of esophageal mucosal integrity, by performing *in vivo* experiments of acid perfusion in rabbits and humans. They also analyzed impedance-pH tracings from patients with GERD. These authors showed that impedance baseline values reflect the status of the esophageal mucosa both in an animal model and in healthy volunteers, indicating that MII is a useful tool to evaluate the esophageal mucosa integrity. They confirmed that patients with erosive and non-erosive esophagitis had a lower impedance baseline compared to healthy volunteers [34].

Further, Kessing et al. [40] described lower values of baseline impedance levels in distal esophagus in patients with abnormal esophageal AET rather than in healthy volunteers (HVs). The authors described a negative correlation between baseline impedance levels and esophageal AET [40]. Woodland et al. [41] observed that, within both NERD and FH, patients who showed a positive acid sensitivity test had lower baseline impedance than those who did not. Of note, the authors found that a subgroup of patients with FH, despite having a normal MII-pH study and a negative

response to proton pump inhibitors (PPIs), had baseline impedance values very similar to those of patients with NERD.

These studies evaluated baseline impedance values during the upright period of 24-h MII-pH analysis. Frequently these authors described some difficulties to obtain data on baseline impedance values excluding frequent swallows and reflux events. We recently dedicated our interest in baseline impedance values, and we decided to calculate the baseline value during overnight rest. It seemed easier and less affected from sampling errors. During sleeping esophageal mucosa collapses on the MII-pH probe, allowing a more accurate assessment of the real impedance in the esophageal mucosa. Nocturnal baseline impedance was assessed from the most distal impedance channel. Three 10-min time periods (around 1.00 am, 2.00 am, and 3.00 am) were selected, and the mean baseline for each period was computed with the aid of the software. Time periods including swallows, refluxes, and pH drops were avoided. The mean of the three measurements was manually calculated to obtain a parameter that we defined mean nocturnal baseline impedance (MNBI). In a large group of patients with GERD typical symptoms, negative endoscopy, and normal pathophysiological characteristics (normal AET and number of refluxes, negative SI and SAP), we observed that patients with a good symptom relief after PPI therapy had lower baseline impedance values than PPI-refractory patients with normal pathophysiological characteristics (FH) [42]. FH patients showed similar baseline value than HVs. Moreover, we observed similar results analyzing PSPW index: it was lower in responders than in nonresponders and in HVs. A direct linear correlation between PSPW and baseline impedance values was found [42].

After that preliminary study, de Bortoli et al. [43] decided to extend these analyses to patients with a 24-h MII-pH diagnosis of hypersensitive esophagus (HE) (normal AET and number of reflux events but positive correlation between symptoms and refluxes as established by both positive SI and SAP analyses) [43]. The authors confirmed previous results observed with MNBI and PSPW index: both parameters were lower in patients with HE and those with positive response to PPI therapy but normal pathophysiological findings (FH-PPI responder) compared to healthy controls and FH-PPI non-responders. These results suggest that both MNBI and PSPW index can be helpful to diagnose GERD in patients with heartburn even when SI and SAP are negative or inconclusive [43].

More recently Frazzoni and coworkers [44] aimed to assess the diagnostic accuracy of MNBI and PSPW index in a large multicenter case series of patients with PPI-responsive heartburn. All patients were evaluated after discontinuing PPI-therapy for 1 month. The authors retrospectively studied 68 patients with erosive esophagitis and 221 patients with NERD and compared their result with those observed in 50 healthy controls. In receiver operating characteristic analysis, the area under curve of the PSPW index (0.977; 95 % confidence interval, 0.961–0.993) was significantly greater than that of the other impedance-pH parameters in identifying patients with reflux disease ( $P < .001$ ). The PSPW index and the MNBI resulted able to identify patients with erosive reflux disease with the highest level of sensitivity (100 % and 91 %, respectively), as well as the 118 pH-positive (99 % and 86 %) and 103 pH-negative (77 % and 56 %) cases of NERD. The PSPW index and

the MNBI identified pH-negative NERD with the highest level of sensitivity; values were 82 % and 52 % for the 65 SAP-positive and/or SI-positive cases and 68 % and 63 % for the 38 SAP-negative and SI-negative cases. Diagnoses of NERD were confirmed by pH-only criteria, including those that were positive on the basis of the SAP or SI, for 165 of 221 cases (75 %) and by impedance-pH criteria for 216 of 221 cases (98 %) ( $P=.001$ ). The authors concluded that the PSPW index and the MNBI increase the diagnostic yield of impedance pH monitoring of patients with reflux disease [44].

Similar results were described by Kandulsky et al. [45]; they observed that baseline impedance values might differentiate patients with ERD or NERD from patients with FH (78 % sensitivity and 71 % specificity) in a population of patients with proton pump inhibitor-refractory reflux related symptoms. Low levels of baseline impedance were associated with greater esophageal acid exposure and dilation of intercellular spaces, confirming that baseline impedance should be considered as a marker of mucosal integrity [45].

Currently, PPI resistance is the real challenge in GERD [46]. However, it has been claimed that between 10 and 40 % of patients with typical reflux symptoms (heartburn/regurgitation) remain symptomatic on a standard dose of PPIs, and many of them will continue to experience symptoms on even high doses of PPIs [47].

What constitutes refractory GERD remains an area of controversy. Most investigators believe that only patients with GERD who exhibit partial or lack of response to PPIs twice daily should be considered as PPI failures [47]. Furthermore, regurgitation persists in many patients despite PPI therapy [48], often awakening patients at night.

Management of PPI-refractory GERD patients is a challenging task. Baclofen could be helpful as add-on therapy with PPIs, but its use is limited by poor tolerability [49] and it is not approved for GERD management. In patients with documented GERD who do not respond sufficiently to PPI therapy, laparoscopic Nissen fundoplication represents the currently suggested treatment modality to overcome PPI failures [50].

Frazzoni et al. [51] aimed to assess reflux parameters in refractory GERD patients before and after EsophyX or laparoscopic fundoplication and their relationship with symptoms. The authors evaluated patients on PPI therapy before intervention and off PPI therapy 3 months after intervention by means of MII-pH monitoring. Distal and proximal refluxes were significantly reduced postoperatively in the surgical but not in the endoscopic (EsophyX) group. The esophageal acid exposure time was normal in 50 % of cases after EsophyX and in 100 % of cases after surgery ( $P=0.033$ ). They concluded that EsophyX fundoplication was significantly less effective than laparoscopic fundoplication in improving reflux parameters and in inducing symptom remission in patients with refractory GERD [51].

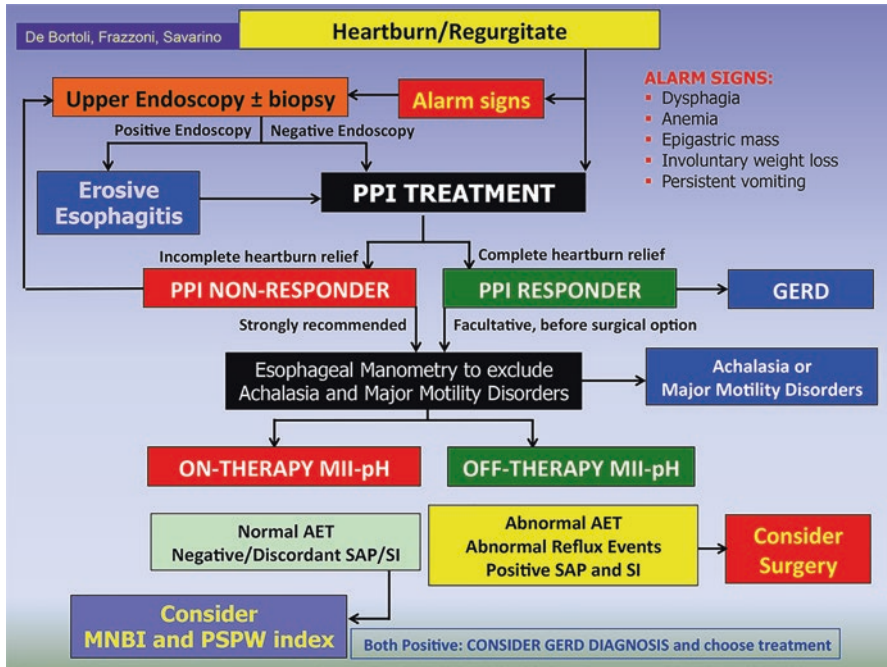
The same working group [52] aimed to evaluate reflux parameters and their relationship with symptoms before and after laparoscopic fundoplication, on and off PPI therapy, respectively, in patients with PPI-unresponsive heartburn/regurgitation and with a positive symptom-reflux association and/or abnormal reflux parameters detected on PPI therapy. The authors described that esophageal AET (100 %) as

well as the number of total (77%) and proximal reflux (95%) events and of acid (92%) and weakly acidic (65%) refluxes decreased significantly after surgery in patients with refractory GERD. The authors concluded that laparoscopic fundoplication improves acid and weakly acidic reflux parameters when compared with PPI therapy and strongly support that surgical option should be considered in PPI failures patients with GERD confirmed with pathophysiological test [52].

In a recent study, normal reflux parameters and sustained symptom remission at a 3-year follow-up, i.e., GERD cure, were achieved with laparoscopic fundoplication in 90% of patients with PPI-refractory GERD as diagnosed by on-PPI impedance-pH monitoring [53]. Interestingly, this study shows that weakly acidic refluxes are the main determinants of PPI refractoriness: preoperatively, positive symptom/reflux indexes and abnormal reflux parameters were mainly associated with weakly acidic refluxes; postoperatively, persistent remission of heartburn/regurgitation was associated with total/subtotal abolition of weakly acidic refluxes [53].

On-PPI impedance-pH monitoring is warranted in all PPI-refractory patients before laparoscopic fundoplication in order to establish a cause-and-effect relationship between reflux and heartburn/regurgitation persisting despite PPI therapy; indeed, no reflux pattern can be demonstrated associated with PPI failure at off-PPI testing [29]. Impedance-pH monitoring should always be preceded by esophageal manometry to rule out severe esophageal motility disorders. Surgery is indicated in patients with abnormal impedance-pH parameters and/or positive symptom-reflux associations. When symptom reflux correlation (SI/SAP) fails, PSPW index and MNBI appear ready for prime time. Their applicability and reproducibility are very high, [44] and few additional minutes only are required for their calculation during visual analysis of tracings. Currently, visual analysis of impedance-pH tracings is necessary because automated software analysis is not accurate enough [54]. PSPW index and MNBI appear particularly useful when GERD diagnosis is in doubt, i.e., when esophageal AET and the number of total refluxes are normal and SAP and SI are negative or discordant, or the patient denies symptoms during the impedance-pH study or admits poor accuracy in symptom recording; in these instances, when PSPW index and/or MNBI values are abnormal, GERD diagnosis cannot be dismissed (Fig. 14.3). SAP and SI should not be abandoned, however, as there is some evidence that they can predict positive outcome following laparoscopic fundoplication [53, 55, 56]. Whether PSPW index and MNBI can predict response to anti-reflux interventions remain an open issue to be addressed in future studies.

To conclude, MNBI and PSPW index might be considered up-and-coming parameters that can be helpful to better investigate patients with GERD-related symptoms, particularly when symptom-reflux association indexes fail to do it. These parameters make pathophysiological sense and certainly deserve a chance in redeeming the clinical value of ambulatory pH-impedance testing. For sure, further researches are needed to determine if normal MNBI and PSPW index in the setting of normal pH and normal conventional impedance parameters would be the benchmark for diagnosis of functional esophageal symptoms. Other confounders in the assessment of these parameters need to be evaluated, for instance, the contribution of abnormal motor function or esophageal dilation. Recently Gyawali [57] suggested that software tools need to be



**Fig. 14.3** Diagnostic algorithm for patients with typical reflux symptoms

developed by companies marketing pH-impedance to simplify calculation of these parameters, as both MNBI and PSPW index need to be rigorously studied and potentially adapted for clinical use in the short term.

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