Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

ORIGINAL ARTICLE

p-ISSN: 2008-2258 e-ISSN: 2008-4234

Reflux definitions in esophageal multi-channel intraluminal impedance

Azra Rasouli[1], Maryam Soheilipour[2], Mostafa Raisi[2], Hossein Rabbani[3], Negar Eghbalifard[4], Peyman Adibi[2]

[1]Isfahan University of Medical Sciences, Isfahan, Iran
[2]Isfahan Gastroenterology and Hepatology Research Center (IGHRC), Isfahan University of Medical Sciences, Isfahan, Iran
[3]Medical Image and Signal Processing Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Aim: In this study, we aim to propose consensus-based interpretations to enhance both automatic, and manual analysis and then present our recommendations about reflux-related variables to enhance Multichannel Intraluminal (MII) measurements.

Background: Multichannel Intraluminal Impedance-pH (MII-pH) monitoring is the most sensible option to evaluate Gastroesophageal Reflux Disease (GERD), specifically for the patients with normal endoscopy findings, and persistent symptoms without response to Proton Pomp Inhibitor therapy. There were only a few studies on the interpretation of reflux events in MII tracings.

Methods: Several 200 episodes of reflux events were reviewed during several meetings in five steps, to discuss and categorize unresolved issues within existing interpretations, and propose technical principles for accurate characterization of reflux events.

Results: In this study, we show that baseline impedance is determined using a moving average procedure to the impedance data of each channel with a time window of 60 seconds based on this finding; a liquid reflux event is defined as a retrograde 50% drop in baseline impedance, gas reflux event is defined as a rapid increase in impedance greater than 5 kΩ, Mixed liquid-gas reflux is defined as gas reflux occurring immediately before or during liquid reflux.

Conclusion: The reliability of final diagnosis is significantly dependent on the accurate detection of reflux events, which is currently confronting technical limitations. A pathological reflux event propagates to at least three of the impedance sites, according to the literature. We think that taking three impedance locations into account might be too strict.

Keywords: Esophageal reflux, Gastroesophageal reflux, Impedance, Swallow.

(Please cite as: **Rasouli A, Soheilipour M, Raisi M, Rabbani H, Eghbalifard N, Adibi P. Reflux definitions in esophageal multi-channel intraluminal impedance. Gastroenterol Hepatol Bed Bench 2023;16(4):408-414. https://doi.org/10.22037/ghfbb.v16i4.2776).**

Introduction

Gastroesophageal Reflux Disease (GERD) is a common digestive disorder defined as a condition of troublesome symptoms or complications developed by regurgitation (1). When there is proof of either mucosal injury or that the patient's symptoms are connected to the stomach contents bathing flow, the diagnosis of GERD is made. However, there isn't a single test that can show both. Mucosal damage is usually observed with endoscopy, while for the patients with persistent GERD symptoms despite acid suppression, current management algorithms propose ambulatory reflux monitoring that, can show whether there is a relationship between the patient's symptoms, and reflux events (2–5). Multichannel Intraluminal Impedance (MII) combined with pH monitoring is the most sensitive method to assess almost all variables associated with reflux episodes, including duration, the type which can be liquid, mixed or liquid-gas, chemical composition, proximal extent, symptom, and body position during each reflux episode (6–8).

A thorough characterization of reflux episodes is necessary for a precise diagnosis. It is interesting to observe that there are several traps when interpreting the various patterns that might be seen in impedance tracings. The interpretation of reflux episodes has technical limitations, such as the reliability of software and the experience of assessors (8–12). Detection of swallows is also of diagnostic value. Ongoing consensus definitions both for reflux, and swallows are required, to

Received: 06 May 2023 *Accepted*: 11 July 2023
Reprint or Correspondence: **Maryam Soheilipour,** *Isfahan University of Medical Sciences, Isfahan, Iran.*
E-mail: maryamsoheilip@med.mui.ac.ir
ORCID ID: 0000-0001-6382-9543

establish definitions to aid automated analysis. Studies defining various patterns reflected by different MII-pH patterns of bolus transits are scant. For the preliminary phase of our study (13), only simple reflux episodes were intentionally chosen to gain an acceptable amount of inter- and intra-observer agreement.

In order to improve both automated and manual analysis, we classified and addressed a number of common problems found in impedance tracings in this research. We also suggested consensus-based interpretations and offered our suggestions for reflux-related variable definitions to improve MII measurements.

Methods

To reach the final statement we developed and performed a logical stepwise method to reach a total consensus in five steps that are described in brief:

First, 100 episodes were randomly selected from 24-hour archived MII-pH data of 8 individuals. Each episode lasted for two minutes, including possible reflux and swallow events.

Two gastroenterologists were asked to independently evaluate 100 MII-pH episodes and identify suspected reflux events based on their prior knowledge. The level of accord reached between the two experts was 92%. Then, a focus group consisting of three gastroenterologists moderated by a medical engineering data scientist (specialized in the field of signal processing), who was in charge of extraction and presentation of "two-minute episodes" of MII-pH tracings, held 10 meetings. The moderator first described the machine's hardware, software, and exact measurement constraints before presenting the episodes with diagnoses that were comparable to those made by the two main gastroenterologists who interpreted them. We started a deep metacognitive discussion on how each person decided and marked the occurrence/non-occurrence of a reflux event, its start point, its endpoint, and as combined versus distinct nearby repetitive ones, and the logic behind the detection of mixed gas-liquid reflux.

During the third phase, those episodes with the incoherent diagnosis were shown on board sessions and each primary team member was asked to think aloud about how and why s/he reached each episode and detected main marking points of reflux events; there was then an open focus group discussion by third gastroenterologist direction to resolve the inter-observer discrepancies, agree on final diagnostic points based on unanimity and to reach a series of common definitions in form of written objective statements. Afterwards, over incremental reading sessions, the coherent reasoning was applied and refined until the final text. Three highly qualified gastroenterologists met to further analyze inconsistently voted incidents, and the start/stop timing of refluxes at each of the six impedance sites was noted.

During the fourth step, a total number of 87 episodes were finally approved by the experts to include a reflux event; these were compared against the automatic report by the commercial software; which could achieve a sensitivity of 84.8%. The total bolus exposure time, reported by the available software was about 30% shorter than the expert's adjusted analysis; after the removal of false automated reports, the difference decreased to 14%. An example of a false negative automated result is shown in Figure 1.

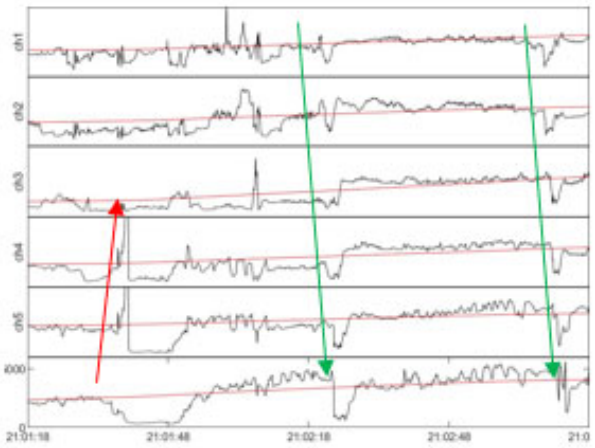

Figure 1. An example of a reflux event that was not detected by software (Red line represents reported base for the recording device). Red and green arrows express reflux and swallows respectively.

In the fifth step of the investigation, 200 episodes, including all sorts of reflux occurrences (chosen at random from 26 individuals' 24-hour archived MII-pH data), were evaluated in several sessions in order to construct a more thorough analysis of impedance tracings. For many reflux episodes, it was challenging to agree between software results and observers among observers. Disagreements between software and manual analysis were mainly attributed to the following reasons:

- Different start and stop times of agreed reflux events, especially for the localization of mixed-type refluxes. There were many cases of prolonged mixed refluxes which were misclassified as short liquid reflux.
- Baseline Impedance (BI).
- Swallows were detected as reflux (FP) events and reflux events were detected as swallows (FN).
- proximal extent of an agreed reflux event

The details of the aforementioned issues are described to recover unresolved issues present in the analysis and interpretation of reflux events in MII-pH tracings. Details of our proposed definitions are provided in Table 1 and Figure 2.

Results

Retrograde bolus movements are attributed to refluxes, whereas ante-grade movements denote swallows. Detected by impedance, type of the reflux is distinguished as either pure liquid or a mixture of liquid and gas (9, 14). When a mixed reflux occurs, a liquid bolus passes through the esophageal lumen, causing a drop in the recorded impedance, meanwhile a gas comes up leading to an increase in the measured impedance for a while and then vanishes moving upward to the proximal sites. Mixed refluxes are more frequent than liquid refluxes; however, details of the mixed-type refluxes have not been identified in the literature.

Statement 1- Liquid reflux is defined as a retrograde 50% drop in impedance starting distally and propagating to at least the next two proximal impedance measuring segments. Gas reflux is defined as a rapid increase in impedance greater than $5^{k\Omega}$, occurring simultaneously in at least two esophageal impedance measuring segments, in the absence of swallowing. Mixed liquid-gas reflux is defined as gas reflux occurring immediately before or during a liquid reflux if the impedance curve reaches back at least to the baseline.

Statement 2- Baseline impedance is investigated by applying a moving average procedure to the impedance data of each channel with a time window of 60 seconds.

Statement 3- In presence of liquid reflux i.e. concurrent with a retrograde drop of impedance to 50% of baseline impedance, the reflux start point is defined as the time when impedance data starts to drop below baseline.

Statement 4- When using impedance data to define reflux, the termination point of any type of reflux is assigned to the point where impedance meets the baseline again.

A concise description of our recommendations for

Table 1. Summary of recommendations on intraluminal impedance-based reflux measurement

• A liquid reflux event is defined as a retrograde 50% drop in baseline impedance starting distally, and propagating to at least the next two proximal impedance measuring segments.
• Gas reflux event is defined as a rapid increase in impedance greater than $5^{k\Omega}$, occurring simultaneously in at least two esophageal impedance measuring segments, in the absence of characteristics of swallowing.
• Mixed liquid-gas reflux is defined as gas reflux occurring immediately before or during a liquid reflux if the impedance curve reaches back at least to the baseline.
• Baseline impedance is determined by applying a moving average procedure to the impedance data of each channel with a time window of 60 seconds.
• In the presence of liquid reflux i.e. concurrent with a retrograde drop of impedance to 50% of baseline, the reflux start point is defined as the time when the impedance curve twitches to drop below baseline.
• When using impedance data to define reflux, the termination point of any type of reflux is assigned to the time when the impedance curve meets the baseline again.
• A reflux event duration i.e. bolus exposure time is the distance from the start to termination points on the baseline curve.
• The duration of significant reflux is always greater than 5 seconds at the most distal impedance measurement site.
• To determine the proximal extent of a reflux event with an unusual pattern at the pharyngeal sites, it is preferred to investigate the distal sites neglecting the two pharyngeal sites.
• To reduce the signal noise effect on measurement, it is allowed to set the stop time of a reflux event at the pharyngeal sites on the stop time of the distal sites.
• Reflux-like patterns and episodes that happen within 5 seconds after a swallow- event should be excluded from further measurements.
• A swallow event pattern might happen within a detected reflux period, and the covering reflux episode should not be excluded from calculations.

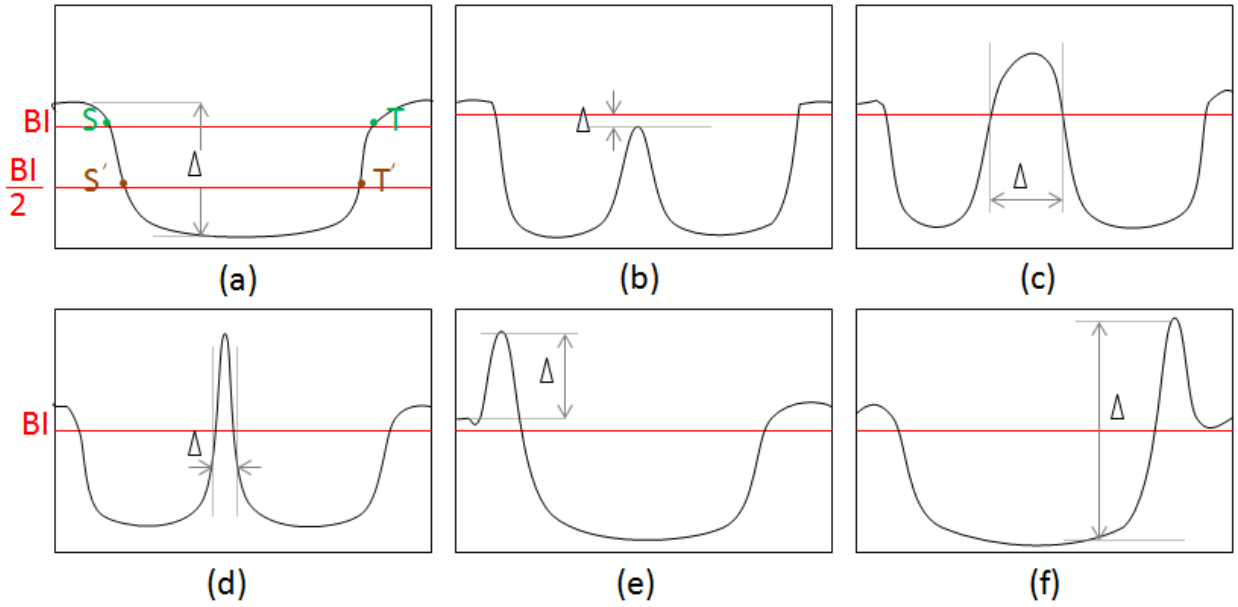

Figure 2. Schematic sketches describing recommended criteria for reflux detection, the vertical and horizontal axis correspond to impedance data at the most distal site and time measures, respectively. For each panel the red solid line is the BI value. Panel (a) describes our recommended amended points for start and stop time of reflux events. Panel (b) is a liquid reflux as impedance value is always below BL. In panel (c), Δ is greater than *du_thre*; therefore the diagram corresponds to two distinct liquid refluxes. Panel (d) shows a mixed reflux as Δ is smaller than *du_thre*. Depending on the amount of Δ, each of panels (e) and (f) might be attributed to liquid (Δ<*I_thre*) or mixed type reflux (Δ> *I_thre*).

the sought-of reflux episodes is presented in Figure 2. The positive variable Δ is correlated to the difference of a unique measure in two different points. Figure 2 discusses the most distal site only; both of the remaining distal sites are supposed to exhibit a drop of impedance greater than 50% of BI.

Panel (a) depicts our amended description for the start and stop points of a reflux event. Similar to the previous, liquid reflux happens when a drop in impedance occurs within at least 3 of the distal sites, rather than the 50% of BI.

Statement 5- A reflux event duration i.e. bolus exposure time is the distance from start to termination points on the baseline curve. The duration of significant reflux is always greater than 5 seconds at the most distal impedance measurement site.

Laryngopharyngeal Sites: The first two proximal impedance values are often very high and artifacts, reflecting the presence of air within the hypopharynx (16) and making it difficult to determine the proximal extent of reflux. We have observed an unusual case resulting from such a noisy condition. The case is depicted in Figure 2 which is very prevalent. In such an occasion, reflux reflects a liquid bolus pattern at the distal sites and then it acts differently at the pharyngeal sites, just like it has been converted to a gas-only reflux. The causal mechanism of this phenomenon is not clear.

Statement 6- To determine the proximal extent of a reflux event with an unusual pattern at the pharyngeal sites, it is preferred to investigate the distal sites neglecting the two pharyngeal sites.

Laryngopharyngeal Duration: In an unusual reflux pattern the duration of reflux at the two pharyngeal sites may be longer than at the distal sites. This was illustrated in the second case of Figure 3. The interpretation of duration may be quite difficult in such a situation.

Statement 7- To reduce the signal noise effect on measurement, it is allowed to set the stop time of a reflux event at the pharyngeal sites on the stop time of the distal sites.

Statement 8- Reflux-like patterns and episodes that happen within 5 seconds after a swallow- event should be excluded from further measurements. A swallow

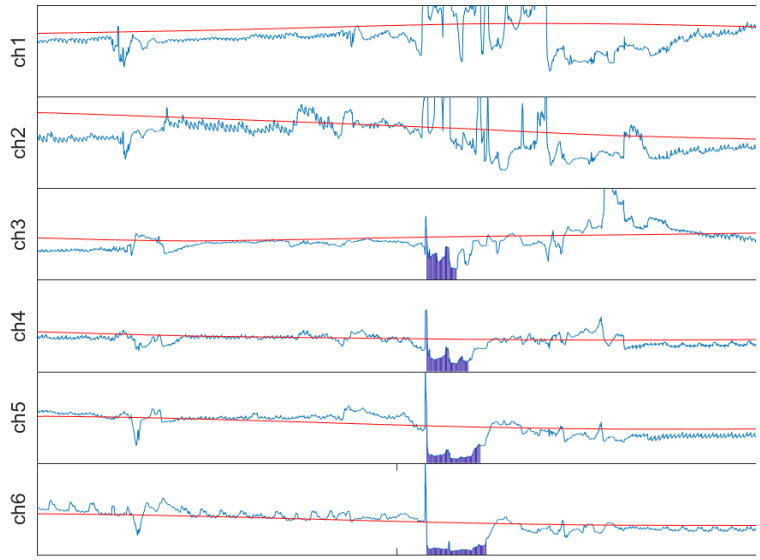

Figure 3. A two-minute interval of MII (Blue patterns) and BI (red curves). The highlighted area represents a pattern at the distal sites which seems to be a liquid reflux, but it starts to act differently at the proximal sites.

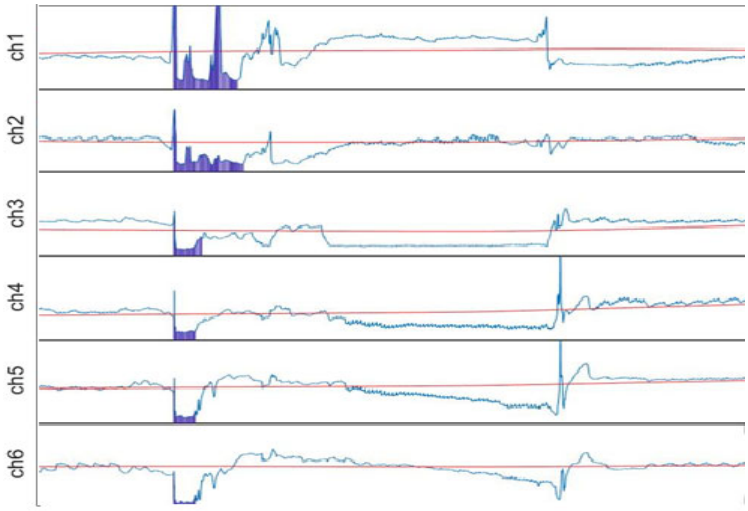

Figure 4. An unusual reflux pattern, with longer duration at pharyngeal sites.

event pattern might happen within a detected reflux period, and the covering reflux episode should not be excluded from calculations.

The panels in Figure 4 describe possible increases within a liquid reflux event. Panel (b) shows liquid reflux as the increased amount has not reached the BI value. In panels (c) and (d) the increased amount has met the BI line, depending on the amount of Δ, the detected pattern could either be correlated to (c) two distinct liquid refluxes (Δ > *du_thre*) or (d) mixed type reflux (Δ < *du_thre*). An amount of 5 seconds is set for the *du_thre* variable.

For the last two panels (e) and (f), the detected reflux episode is of type mixed, if the amount of increase Δ, is greater than the *I_thre* threshold. The amount Impedance threshold was set to $5^{k\Omega}$.

Discussion

Baseline Impedance (BI): Electrical conductivity of an empty esophageal lumen is considered as BI value, which is relatively stable and has a value between $2^{k\Omega}$ to $4^{k\Omega}$ (9). BI value may change during a 24-hour study and is expected to be higher in laryngeal sites. When a bolus passes through the esophageal lumen, it can

either increase or decrease the measured impedance, according to its physical state of it. Some studies have reported their method to calculate BI as a constant value, for long durations of an hour namely (11, 15). This constant amount for BI does not apply to automated reflux investigation schemes. Therefore, the problem to investigate BI through recorded impedance signals remains unresolved and has not been addressed in the literature. Besides, some studies argue with the 50% reduction of BI, as they believe that there are important reflux patterns ruled out, considering this stringent amount (10).

Bolus Exposure: Exposure of reflux is defined as the time interval between bolus entry to clearance which is measured at the most distal impedance site (14). Bolus entry or the start time of the reflux is distinct. Given BI, the start of reflux can be assessed by knowing the time when the impedance signal meets 50% of BI. Our suggestion for the start points has slightly deviated from current routine measurements.

In a study, the stop time of acid reflux was defined as the point where acid meets pH 4 again, after at least 5 seconds (14). Our suggestion for the sought of both start and stop time is to investigate impedance data because of two reasons. First, there are many cases of non-acid reflux episodes that cannot be detected by pH tracings. Second, the pH sensor shows a delay compared to impedance electrodes as the pH probe detects even small acid resides (14), which may lead to an overestimated exposure time.

Duration Margins: The maximum duration for reflux patterns at different impedance sites (including both liquid and mixed types) need to be established, evaluating not only the concurrent impedance and pH tracings but also the physiology and anatomical characteristics of the esophagus and lower esophageal sphincter (LES). The maximum duration of our dataset belonged to mixed reflux and was about 37.1 seconds. To establish the maximum margin, we believe more episodes should be investigated. However, we proposed the minimum margin considering the physiologic properties and clearance mechanism of the esophagus.

Swallows: Contrary to refluxes, ante-grade patterns refer to swallows. A swallow is defined as an antegrade drop of impedance initiated from the most proximal site flowing toward the most distal site. Identification of swallows is also important, at least due to three reasons, first, to exclude unknown cases from detected refluxes, Unknown cases refer to patterns propagating in both retrograde and ante-grade directions, where a reflux event coincides with a swallow event. These unknown cases should further be excluded from the detected reflux class. Second, to calculate the new post-reflux swallow-induced peristaltic wave (PSPW) index (17), and last, to associate each swallowing event to symptoms for the assessment of GERD (12).

Conclusion

The reliability of final diagnosis is significantly dependent on the accurate detection of reflux events, which is currently confronting technical limitations. Based on the literature, a pathological reflux event propagates to at least three of the impedance sites. We believe that considering three impedance sites might be too stringent.

We also suggest examining the usefulness of two new indices. First, computes total Bolus Exposure Time (BET) from impedance tracings within the whole 24 hours of ambulatory monitoring and computes the summation of Area-Under-Curve (AUC) for each of the reflux episodes through all disposed of impedance sites. Impedance and pH measurements give no identification of the volume of the refluxate, as such, similar drops are observed for boluses with very different volumes (10). In addition, for the prevalent mixed-type GERs, the proportion of the liquid versus gas cannot be identified to be able to assess the volume of the reflux content. We plan to investigate the usefulness of the proposed AUC index in our future works.

Conflict of interests

The authors indicate no potential conflicts of interest.

References

1. Fazel M, Keshteli AH, Jahangiri P, Daneshpajouhnejad P, Adibi P. Gastroesophageal reflux disease in Iran: SEPAHAN systematic review No. 2. Int J Prev Med 2012;3:10-7.

2. Bredenoord AJ, Smout A, Tack J. A guide to gastrointestinal motility disorders. Springer; 2016. Available at: https://link-springer-com.ezproxy1.library.usyd.edu.au/content/pdf/10.1007%2F978-3-319-26938-2.pdf

3. Karamanolis G, Kotsalidis G, Triantafyllou K, Polymeros D, Gaglia A, Fessatou S, et al. Yield of

combined impedance-pH monitoring for refractory reflux symptoms in clinical practice. J Neurogastroenterol Motil 2011;17:158–63.

4. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation global study. Gastroenterology 2021;160:99–114.

5. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. Best Pract Res Clin Gastroenterol 2010;24:923–36.

6. Lee BE, Kim GH, Ryu DY, Kim DU, Cheong JH, Lee DG, et al. Combined dual channel impedance/pH-metry in patients with suspected laryngopharyngeal reflux. J Neurogastroenterol Motil 2010;16:157–65.

7. Sung HJ, Cho YK, Moon SJ, Kim JS, Lim CH, Park JM, et al. Role of acid and weakly acidic reflux in gastroesophageal reflux disease off proton pump inhibitor therapy. J Neurogastroenterol Motil 2012;18:291–7.

8. Chae S, Richter JE. Wireless 24, 48, and 96 Hour or Impedance or Oropharyngeal Prolonged pH Monitoring: Which Test, When, and Why for GERD? Curr Gastroenterol Rep 2018;20:52. Available from: https://doi.org/10.1007/s11894-018-0659-0.

9. Ghoshal UC. Evaluation of gastrointestinal motility and its disorders. Springer; 2016.

10. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024–31.

11. Tenca A, Campagnola P, Bravi I, Benini L, Sifrim D, Penagini R. Impedance pH monitoring: Intra-observer and inter-observer agreement and usefulness of a rapid analysis of symptom reflux association. J Neurogastroenterol Motil 2014;20:205–11.

12. Woodley FW, Ciciora SL, Vaz K, Williams K, Di Lorenzo C, Jadcherla S. Novel use of impedance technology shows that esophageal air events can be temporally associated with gastroesophageal reflux disease-like symptoms. J Pediatr Gastroenterol Nutr 2020;70:7–11.

13. Rasouli A, Rabbani H, Raisi M, Soheilipour M, Adibi P. Liquid gastroesophageal reflux characterization by investigating multichannel intraluminal impedance-pH monitoring data. 2019;4636–9.

14. Cho YK. How to interpret esophageal impedance pH monitoring. J Neurogastroenterol Motil 2010;16:327.

15. Chun YJ, Choi MG, Kim HH, Cho YK, Ku A. Is the impedance baseline helpful in the evaluation of globus patients? J Neurogastroenterol Motil 2015;21:390–7.

16. Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, et al. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol 2013;11:366–72.

17. Cho YK, Lee JS, Lee TH, Hong SJ, Park SJ, Jeon SR, et al. The relationship of the post-reflux swallow-induced peristaltic wave index and esophageal baseline impedance with gastroesophageal reflux disease symptoms. J Neurogastroenterol Motil 2017;23:237–44.