

The Role of Distal Mean Nocturnal Baseline Impedance in Differentiating GERD Phenotypes

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ABSTRACT

Background & Aims: Gastroesophageal reflux disease (GERD) is one of the most frequent digestive pathologies. The current diagnosis of GERD either by trial of proton pump inhibitors (PPIs), endoscopy or by multichannel impedance pH study (MII/pH) has limitations. Our study aims to show if mean nocturnal baseline impedance (MNBI) can differentiate between the GERD phenotypes.

Methods: We recruited 62 patients who underwent upper digestive endoscopy and MII/pH, with some patients undergoing esophageal manometry to exclude motility disorders. Patients were separated into 4 GERD phenotypes: erosive reflux disease (ERD), non-erosive reflux disease (NERD), reflux hypersensitivity (RH) and functional heartburn (FH). Proximal MNBI was calculated as the mean value of the proximal 2 channels (Z1 and Z2), and distal MNBI was calculated as the mean value of the distal 4 channels (Z3, Z4, Z5, Z6).

Results: Distal MNBI can help distinguish the abnormal acid exposure time (AET) phenotypes (ERD, NERD) from normal AET phenotypes (RH, FH) with a decent performance (AUROC 0.857). Distal MNBI has good accuracy in separating ERD from other phenotypes (AUROC 0.872). Furthermore, distal MNBI can differentiate FH from ERD, NERD, RH with good accuracy (AUROC 0.879), and on top of that is able to separate FH from RH (AUROC 0.817).

Conclusions: Our study showed that distal MNBI is a good method of differentiating GERD phenotypes and should be taken into consideration in future studies to assess its validity in helping physicians make the correct diagnosis.

Key words: GERD – NERD – MNBI – reflux hypersensitivity – functional heartburn.

Abbreviations: AET: acid exposure time; ERD: erosive reflux disease; FH: functional heartburn; GERD: gastroesophageal reflux disease; MII/pH: multichannel impedance pH study; MNBI: mean nocturnal baseline impedance; NERD: non-erosive reflux disease; RH: reflux hypersensitivity; SAP: symptom association probability; SI: symptom index.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most frequent digestive pathologies encountered by medical professionals in their practices [1]. It is defined by the most recent American College of Gastroenterology guidelines as “the presence of characteristic mucosal injury seen at endoscopy and/or abnormal esophageal acid exposure demonstrated on a reflux monitoring study” [2].

It represents an important part of public health with an enormous economic impact for the healthcare system and the global population [3]. The prevalence of GERD is on the rise globally due to obesity epidemic and the dietary changes of the last decades [3]. It can affect patients of all ages and genders, with an estimated global prevalence of around 14% [1]. The economic impact is vast and on the rise in recent years, some studies putting the economic burden at around 10 billion dollars per year due in large part to the expenses associated with treatment and diagnostic methods employed, consequently making GERD one of the most expensive digestive pathologies in the world [4]. The current diagnosis of GERD either by trial of proton pump inhibitors (PPIs), endoscopy or by multichannel impedance pH study (MII/pH) has limitations [5].

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Patients with GERD can be divided based on upper endoscopy results in patients with erosive reflux disease (ERD) and non-erosive reflux disease (NERD) [5-7]. Patients with ERD have the following upper endoscopy findings: Los Angeles grade C, D esophagitis, peptic strictures or Barrett's esophagus, while Los Angeles grade A and B esophagitis is considered borderline evidence for ERD [5, 7].

Using MII/pH, NERD can be further classified in 3 phenotypes: true NERD, reflux hypersensitivity (RH) and functional heartburn (FH) [6-8]. An abnormal acid exposure time (AET) defined as over 6% is currently the most reliable pH study parameter to define NERD [7, 9, 10]. Meanwhile, RH is defined by a normal AET (AET under 4%) with a symptom association probability (SAP) of over 95% and symptom index (SI) of over 50% [7]. Functional heartburn is characterized by a normal AET (under 4%), a SAP of under 95% and a SI of under 50% [7, 9, 10].

Although total AET is used as a predictive factor for anti-reflux therapies, it has significant day-to-day variability [11, 12].

Consequently, new parameters have been proposed to help facilitate the different GERD phenotypes, such as mean nocturnal baseline impedance (MNBI) which has less day-to-day variability compared to AET [13, 14]. No formal guidelines have been published on the proper way to measure MNBI; most have focused on measuring MNBI at 3 cm and 5 cm above the LES [13, 15-17]. Our study investigated if MNBI could differentiate between the GERD phenotypes.

METHODS

We conducted a retrospective analysis of prospectively collected data of 116 consecutive patients with heartburn; we included patients between September 2020 until December 2021 from the Gastroenterology Department at the Bucharest Emergency University Hospital, Romania. The study was

achieved in conformity with the Declaration of Helsinki and was authorized by the local Ethics Committee. All patients in the study provided informed consent prior to study enrolment. We included patients over the age of 18 with findings that suggested GERD based on symptoms (heartburn, regurgitation, non-cardiac epigastric chest pain), MII/pH or endoscopy findings. All patients underwent a complete medical exam with detailed medical history, dietary habits, alcohol consumption, smoking history. All patients underwent upper digestive endoscopy and MII/pH, with some patients undergoing esophageal manometry to exclude motility disorders. The impedance-pH catheters allowed for monitoring of intraluminal impedance changes at 3, 5, 7, 9, 15, and 17 cm and intraluminal pH changes at 5 cm above the lower esophageal sphincter according to the endoscopic measurements that were performed beforehand.

We excluded patients on PPIs in the last 2 weeks prior to MII/pH (n=20), history of heavy alcohol use (over 30-40 grams per day, n=10), patients with esophageal motility disorders (n=5), surgical history of the esophagus or the stomach (n=3), esophageal varices (n=5), history of stroke or severe neurological conditions (n=5) and otolaryngologic disorders (n=6). 62 patients were further investigated. Patients were separated into 4 GERD phenotypes: ERD, NERD, RH, FH (Fig. 1).

Gastroesophageal reflux disease phenotypes were diagnosed according to Lyon Consensus and Roma IV criteria [5, 7, 9]. Erosive reflux disease was diagnosed by upper digestive endoscopy (esophagitis LA Grade A, B, C, D; peptic strictures, Barrett's esophagus) and with AET of more than 6%. Patients with normal upper digestive endoscopy findings and abnormal AET (>6%) were classified as NERD.

Patients with normal endoscopy and a normal AET (under 4%), with SAP over 95% and SI over 50% were classified as RH. Patients with normal AET, SAP under 95% and SI under 50% were defined as FH. Patients with borderline AET (between 4-6%) were excluded from the study.

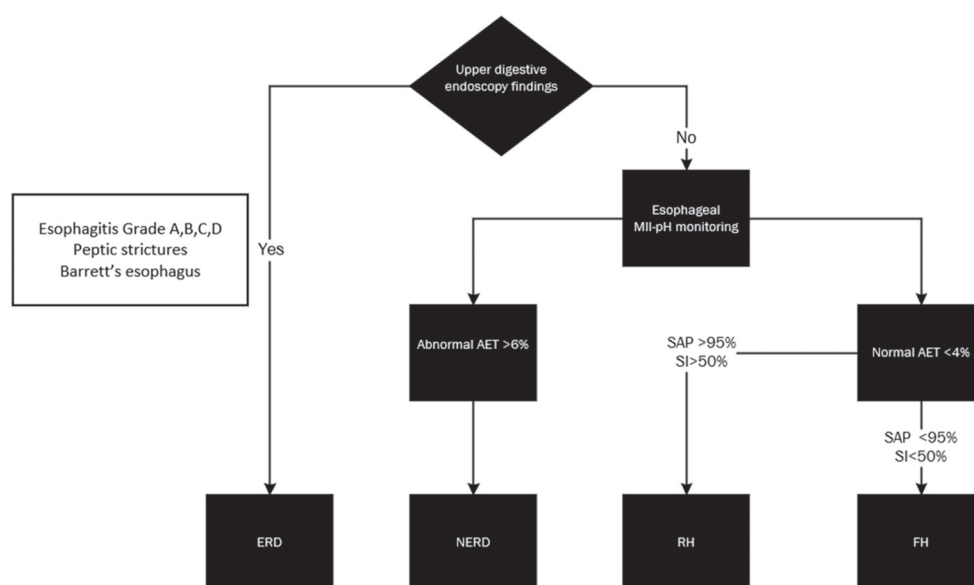


Fig. 1. Flowchart to diagnose GERD phenotypes. AET: acid exposure time; SAP: symptom association probability; SI: symptom index; ERD: erosive reflux disease; NERD: non-erosive reflux disease; RH: reflux hypersensitivity; FH: functional heartburn.

Multichannel Intraluminal Impedance and pH Monitoring

All patients underwent MII/pH using the Ohmega-Ambulatory Impedance-pH Recorder device (MMS, Netherlands) which contain a catheter with six impedance and two pH channels. All patients had to stop treatment with proton pump inhibitors and H₂ histamine receptor antagonist 14 days prior to MII/pH. Patients were instructed how to use the event buttons in order to record meal time, position (supine or upright) and symptom episodes. Recording lasted approximately 24 hours and data was analyzed by physicians.

Software provided by Ohmega MMS was used to calculate the DeMeester score, AET, total number of reflux episodes, SAP and SI. The catheter was positioned trans-nasally and MNBI was measured at all impedance channels (Z1-17 cm, Z2-15 cm, Z3-9cm, Z4-7cm, Z5-5cm, Z6-3cm distance from lower esophageal sphincter) as the mean value from 3 distinct timeframes at 1:00 AM, 2:00 AM, 3:00 AM across stable nocturnal 10-minute periods [14].

Proximal MNBI was calculated as the mean value of the proximal 2 channels (Z1 and Z2), and distal MNBI was calculated as the mean value of the distal 4 channels (Z3, Z4, Z5, Z6) [17].

Statistical Analysis

IBM SPSS 23 (Statistical Package for the Social Sciences Inc, IBM corporation, Armonk, NY) and Microsoft Excel (Microsoft Corporation, Redmond, WA) were used to analyze the data. The parameter values are shown as the median and interquartile range. Groups were compared using the MannWhitney U test with the Bonferroni correction.

Diagnostic performance of parameters was assessed by area under the ROC curve (AUROC) analysis. The cut-off values were selected based on the ROC curve with the optimal sensitivity and specificity and the best overall diagnostic performance. A p value of under 0.05 was defined as statistically significant.

RESULTS

Patients were separated by phenotypes and their characteristics are presented in Table I. A total of 62 patients were included, 30 patients were diagnosed with ERD, 11 with NERD, 10 with RH and 11 with FH. Between these groups there was significant statistical differences in proximal MNBI, distal

MNBI, DeMeester score and AET, there were no correlations between age, gender or BMI.

A stepwise approach to distinguish the diagnostic accuracy of proximal MNBI, distal MNBI, DeMeester score and AET was used. On univariate analysis, all the parameters, proximal MNBI ($p<0.001$), distal MNBI ($p<0.001$), DeMeester score ($p<0.001$) and AET ($p=0.05$) were associated with the presence of ERD, but on multivariate analysis only distal MNBI was associated with the existence of ERD ($p=0.002$). Fig. 2 shows the AUROC of proximal and distal MNBI in differentiating ERD from the other phenotypes. Proximal MNBI had a AUROC of 0.712 (CI 95%: 0.528-0.801), while distal MNBI had a superior AUROC of 0.872 (95%CI: 0.781-0.963). For a cut-off of value of 1683 Ω , distal MNBI was able to distinguish ERD from NERD, RH, FH with a sensitivity of 82% and a specificity of 80%.

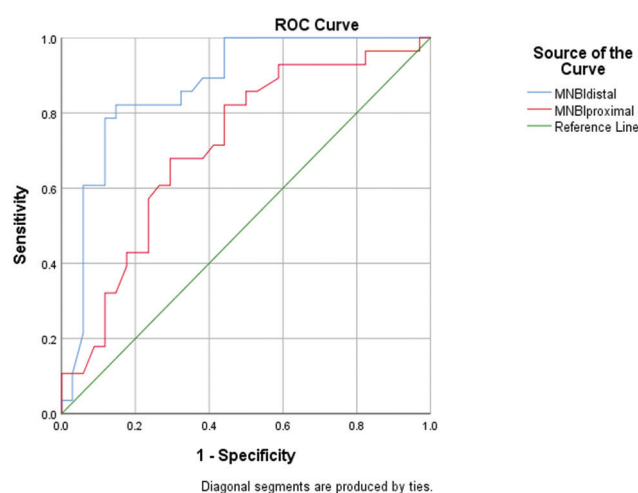


Fig. 2. Distinguish ERD from NERD, RH, FH. For abbreviations see Fig 1.

The next step was to ascertain the diagnostic accuracy of distinguishing normal AET phenotypes (FH and RH) from abnormal AET phenotypes (ERD and NERD) of different parameters. On univariate analysis all the parameters proximal MNBI ($p<0.001$), distal MNBI ($p<0.001$), DeMeester score ($p<0.001$) and AET ($p<0.001$) were associated with the presence of ERD and NERD, but on multivariate analysis only distal MNBI had a statistically significant correlation ($p<0.001$). Fig. 3 illustrates the AUROC of proximal and distal MNBI for separating normal AET phenotypes (FH and

Table I. Characteristics of patient population (n=62)

Characteristics	ERD (n=30)	NERD (n=11)	RH (n=10)	FH (n=11)	P- value
Age (years)	53.9 $\pm$ 14	48.7 $\pm$ 9.9	44.9 $\pm$ 11.5	49.27 $\pm$ 12	0.330
Gender M/F	12/18	7/4	6/4	5/6	0.550
BMI	24.1 $\pm$ 2	25 $\pm$ 3.6	24.3 $\pm$ 3.8	23 $\pm$ 1.95	0.589
DeMeester Score	188 $\pm$ 67	136 $\pm$ 82.8	4 $\pm$ 1.72	2 $\pm$ 1.6	0.001
AET (%)	57.3 $\pm$ 24.9	46.6 $\pm$ 27.3	3.8 $\pm$ 1.8	3.6 $\pm$ 1.62	0.003
MNBI (Ω)					
Proximal MNBI (Ω)	1752 $\pm$ 718	1806 $\pm$ 708	2099 $\pm$ 743	2295 $\pm$ 440	0.023
Distal MNBI (Ω)	1213 $\pm$ 716	1510 $\pm$ 806	2036 $\pm$ 412	2457 $\pm$ 380	>0.001

BMI: body mass index; AET: acid exposure time; MNBI: mean nocturnal baseline impedance.

RH) from abnormal AET phenotypes. Proximal MNBI had a AUROC of 0.682 (CI 95%: 0.545-0.818), while distal MNBI had a superior AUROC of 0.857 (95%CI: 0.762-0.952). For a cut-off value of 1865 Ω , distal MNBI was able to separate normal AET phenotypes (FH and RH) from abnormal AET phenotypes (ERD and NERD) with a sensitivity of 85.7% and specificity of 80%.

The last step was to ascertain if distal MNBI was able to distinguish FH from RH, ERD and NERD. Distal MNBI was the single parameter able to diagnose FH after multivariate statistical analysis ($p=0.001$) from the other phenotypes. The AUROC was 0.879 (CI 95%: 0.789-0.969) for distal MNBI, which was superior to proximal MNBI with an AUROC of 0.687 (95%CI: 0.545-0.829) (Fig. 4). A cut-off value of 2280 Ω for distal MNBI was able to distinguish FH from RH, ERD, NERD with a sensitivity of 84% and a specificity of 86%.

Finally, we tried to determine if MNBI could be used to differentiate between FH and RH. Distal MNBI was able to separate the two phenotypes with an AUROC of 0.817 (CI 95%: 0.635-1) as shown in Figure 5. A distal MNBI cut-off value of 2164 Ω was capable of separating FH from RH with a sensitivity of 84.6% and a specificity of 63%.

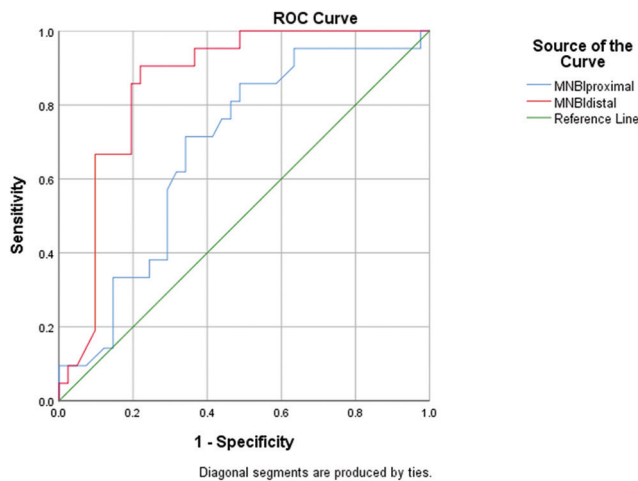


Fig. 3. Distinguish normal AET (FH, RH) from abnormal AET (ERD, NERD) phenotypes. For abbreviations see Fig. 1.

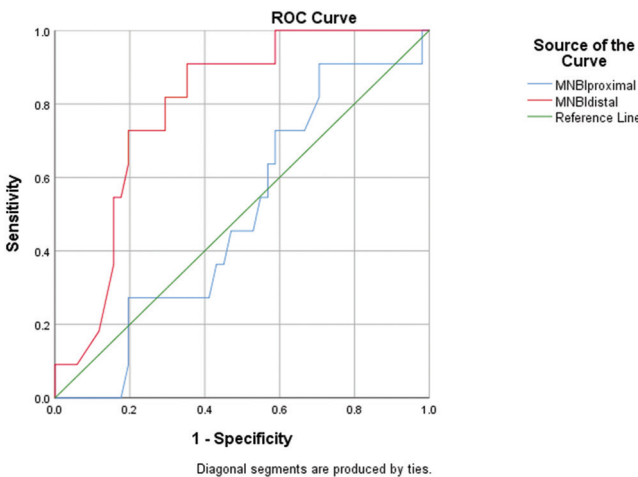


Fig. 4. Distinguish FH from RH, ERD, NERD. For abbreviations see Fig. 1.

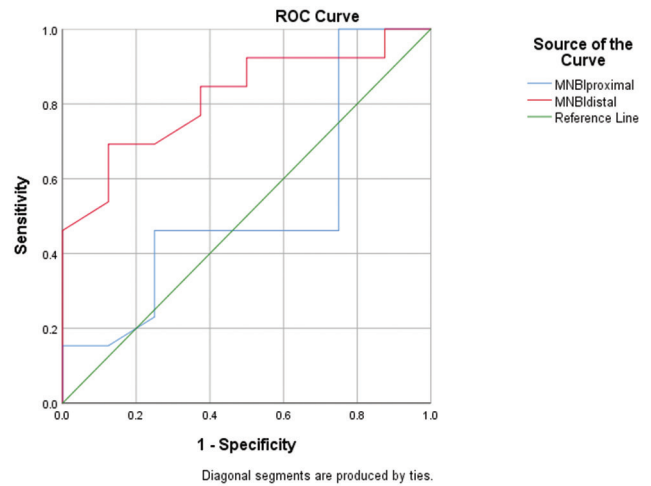


Fig. 5. Distinguish functional heartburn from reflux hypersensitivity.

DISCUSSION

Our study showed that distal MNBI could be a good parameter for aiding the differentiation of GERD phenotypes (Table II). Distal MNBI can help distinguish the abnormal AET (>6%) phenotypes (ERD, NERD) from normal AET (<4%) phenotypes (RH, FH) with a decent performance (AUROC 0.857). Distal MNBI has good accuracy in separating ERD from other phenotypes (AUROC 0.872). Furthermore, distal MNBI can differentiate FH from ERD, NERD, RH with good accuracy (AUROC 0.879), and on top of that is able to separate FH from RH (AUROC 0.817).

Baseline esophageal impedance values have been shown to be correlated with histologic evidence of acid injury of the esophageal mucosa [18]. Unfortunately, baseline esophageal values are influenced by swallow and the reflux of gases or liquids a lot during the day, these variations occur less at nighttime which is why measurements taken during these periods have higher correction rates. Thus, MNBI is more stable over time and reflects the status of esophageal mucosal integrity better at nighttime.

Previous studies have demonstrated that MNBI was correlated to histological changes in the esophageal mucosa, patients with low values of MNBI like those found in ERD had wider intercellular spaces in the epithelium and tighter junction proteins like claudin-1 [18]. Studies also demonstrated that MNBI was negatively correlated with acid exposure, on top of histological modifications [13, 14, 18]. Data has been slowly building up, advocating for MNBI as diagnostic tool for excluding reflux disease. Two separate European studies found that MNBI could exclude the presence of reflux disease with good accuracy [5, 13, 14]. Another study, this time conducted in an Asian population by Zhong et al. [18], demonstrated the same principle.

Previous studies have also demonstrated that MNBI was a good method of differentiating between GERD phenotypes [15, 17, 19-21]. Similar to our study, Hoshikawa et al. [19] found that MNBI measured at 3 cm or 5 cm above the LES was able to separate abnormal AET phenotypes (ERD and NERD) from normal AET (RH and FH) phenotypes [19]. In that particular study MNBI measured at 3 cm above the LES had a sensitivity

Table II. Distal MNBI results for separating GERD phenotypes

Distal MNBI	AUROC	Cut-Off	Sensitivity	Specificity
Separate ERD from NERD, RH, FH	0.872	1683 Ω	82%	80%
Separate AET abnormal (ERD, NERD) from AET normal (FH, RH)	0.857	1865 Ω	85.7%	80%
Separate FH from RH, ERD, NERD	0.879	2280 Ω	84%	86%
Separate FH from RH	0.817	2164 Ω	84.6%	63%

MNBI: mean nocturnal baseline impedance; For abbreviations see Fig. 1.

of 82.5% and a specificity of 89.7% for a cut-off value of 1785 Ω , while MNBI measured at 5 cm had a sensitivity of 80% and specificity of 90% for a cut-off value of 1943 Ω ; these cut-off values were similar to those in our study [19]. While looking at other GERD phenotypes, one study performed in Korea found that NERD could be differentiated from RH and FH with good accuracy (sensitivity 83%, specificity 69%) for a cut-off value of 2125 Ω , values which were slightly higher than in our study [22].

Functional heartburn seems to be an intriguing GERD phenotype to diagnose. From a histological point of view, it has less dilated intercellular spaces than ERD and NERD, but if MNBI is correlated to these histological changes remains to be seen as very few studies exist [16, 17, 23]. Distal MNBI was able to distinguish FH from other GERD phenotypes in a study with an Asian population with good accuracy (AUROC 0.721) while using a cut-off value of 1890 Ω , which was lower than the cut-off used in our study [17]. Yoshimine et al. [16] revealed that MNBI was also useful in distinguishing FH from PPI-refractory NERD with an AUROC of 0.73 in an Asian population. Similarly, this time looking at a European population (Germany), Kandulski et al. [23] found that MNBI could separate NERD from FH with an AUROC of 0.73 while using a cut-off value of 2100 Ω (sensitivity 79%, specificity 71%). Interestingly, another European, this one done in Italy by Tenca et al. [15] showed that MNBI can help separate FH from NERD with a much higher accuracy (AUROC 0.960).

When it comes to separating the two normal AET phenotypes (RH and FH) from each other, results using MNBI have been varied [20, 21]. Frazzoni et al. [20] found that MNBI can differentiate RH from FH with a good accuracy (AUROC 0.864), while Gao et al. [21] found that MNBI was a poor method of separating the two entities (AUROC 0.643). Gomes et al. [24] also found no significant differences between RH and FH using MNBI.

The concept of using proximal MNBI calculated as the mean value of the proximal 2 channels and distal MNBI calculated as the mean value of the last 4 distal channels has been used in another study by Patel et al. [25] based on a North American population. The authors found that lower distal MNBI values, but not proximal MNBI values, were associated with increased pathologic esophageal acid exposure and better symptomatic outcomes [25]. Thus, MNBI may complement AET, especially if AET alone is inconclusive for diagnosing reflux disease [25].

It is important to point out that MNBI values in the distal esophagus has significant differences based on geographical region, hence the wide range of cut-off values found in studies

[26]. Distal MNBI values were higher in Asia and South Africa compared to other regions [26]. Diet, genetic and cultural differences seem to play a huge part in MNBI values across the globe, making it even more difficult to ascertain its validity as a diagnostic tool [24]. There also seem to be important discrepancies of MNBI values based on the medical devices used to record this parameter [26]. The MMS apparatus for example, which is the same device used in our study recorded higher MNBI values especially at 5 cm above the lower esophageal sphincter compared to other medical devices [26]. Lastly, there are different ways of measuring and defining MNBI, some studies measured MNBI just at 3 cm above the lower esophageal sphincter, while others at 5 cm, and some like our study used many references point to calculate an average [25, 27, 28]. No official guidelines have been published for a correct recording of MNBI. Further studies are required to determine the usefulness of MNBI in differentiating GERD phenotypes and different reference points from 3 cm to 17 cm above the LES need to be explored to assess their accuracy.

Our study has some limitations. Firstly, we had a very small cohort and all the research was performed in one medical institution. Secondly calculation of MNBI at different reference points plus calculation of proximal and distal MNBI is a time-consuming event that requires careful attention being prone to human error, in the future this problem could be solved with simple software updates implemented by MII/pH software producers. Thirdly, we observed that the patients with abnormal AET phenotypes (ERD and NERD) had a significantly high AET. This could potentially be attributed to specific dietary habits related to their geographical location, discrepancies in the measurements taken by the MMS apparatus due to high acid exposure or the fact that endoscopy guided the placement of the MII/pH catheter. Many of the patients in our study had a habit of drinking coffee and fizzy drinks that can cause gastroesophageal reflux. They also consumed a lot of fatty, spicy foods (such as hot peppers, garlic, pepper), chocolate and alcoholic beverages like beer or wine that can relax the lower esophageal sphincter and induce reflux. Smoking was another common factor among the patients we studied as most of them were smokers which may have contributed to high AET values [29].

CONCLUSIONS

Our study showed that distal MNBI is a good method of differentiating GERD phenotypes and should be taken into consideration in future studies to assess its validity in helping physicians make the correct diagnosis.

Conflicts of interest: None to declare.

Authors' contribution: R.S. and C.B.F. conceived and designed the study. R.S. and R.P. collected and analyzed the data, drafted the manuscript and revised it. C.B.F. supervised the study and revised the manuscript critically for important intellectual content. All the authors read and approved the final version of the manuscript.

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