



Esophageal Nocturnal Baseline Impedance and Post-reflux Swallow-induced Peristaltic Wave Index in Identifying Proton Pump Inhibitor-refractory Non-erosive Reflux Disease

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Background/Aims

Esophageal mean nocturnal baseline impedance (MNBI) levels and post-reflux swallow-induced peristaltic wave (PSPW) index could increase the diagnostic value of 24-hour multichannel intraluminal impedance and pH monitoring in patients with gastroesophageal reflux disease. This study aims to compare the MNBI and PSPW index in patients with no evidence of erosive reflux disease.

Methods

Impedance-pH monitoring tracings from 70 patients, 50 with non-erosive reflux disease (NERD) and 20 with functional heartburn (FH), were reviewed. According to proton pump inhibitors (PPI) treatment response, NERD patients were divided into NERD/PPI responders and NERD/PPI nonresponders. MNBI, PSPW index, and intercellular spaces were measured and compared among each group.

Results

MNBI values and PSPW index were lower in NERD patients than in FH ($P < 0.01$ and $P < 0.05$, respectively). MNBI positively correlated with PSPW index ($r = 0.525$, $P < 0.001$). NERD/PPI responders had lower MNBI values and PSPW index compared to NERD/PPI nonresponders (both $P < 0.01$). MNBI and PSPW index distinguished NERD from FH patients with an area under the curve of 0.914 and 0.677, respectively. Wider intercellular space could be identified in patients with NERD ($P < 0.01$).

Conclusion

MNBI and PSPW index may differentiate NERD from FH patients and relate to PPI treatment efficacy in patients with NERD.

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Key Words

Electric impedance; Gastroesophageal reflux; Intercellular spaces; Proton pump inhibitors

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Introduction

Among patients with typical gastroesophageal reflux disease (GERD) symptoms, non-erosive reflux disease (NERD) patients with no evidence of esophageal injury under endoscopy account for the majority.^{1,2} Patients with heartburn symptoms are heterogeneous, some of which are functional heartburns (FH).³ Patients with FH assessed using impedance-pH monitoring have normal esophageal acid exposure and normal symptom association analysis.⁴ The diagnosis of FH needs to be considered when patients have no visible esophageal mucosal damage at routine endoscopy. Proton pump inhibitors (PPIs) are used extensively for the treatment of GERD, but a large number of patients have persistent symptoms despite PPI therapy,⁵ especially patients with NERD.^{6,7} The underlying mechanisms accounting for PPI failure in NERD patients have been a focused issue.

Multichannel intraluminal impedance and pH monitoring (MII-pH monitoring) detects reflux episodes including acid reflux, weakly acid reflux, and alkaline reflux.^{8,9} Recently, besides the traditional reflux events and acid exposure time, several novel multichannel intraluminal impedance and pH (MII-pH) metrics have been proposed. Baseline impedance reflects the electrical conductivity and mucosal integrity of the esophageal wall.¹⁰ Previous studies revealed that mean nocturnal baseline impedance (MNBI) correlated with esophageal histopathologic changes and was lower in GERD patients than in FH patients and healthy subjects.^{11,12} Post-reflux swallow-induced peristaltic wave (PSPW) index could be used to assess the impaired chemical clearance in patients with GERD, which is significantly lower in NERD patients than FH patients.¹³ It was demonstrated that PSPW index and MNBI increased the diagnostic accuracy of MII-pH monitoring in cases with PPI responsive heartburn.¹⁴ Frazzoni et al¹⁵ found that 76.0% and 92.0% of PPI-responsive heartburn cases had abnormal MNBI and PSPW index. However, Ribolsi et al¹⁶ found no difference of MNBI between PPI responders and nonresponders in NERD patients and that baseline impedance could not predict PPI response in NERD patients. So far, the role of PSPW index and MNBI in PPI-refractory NERD patients has not been investigated well.

We compared MNBI, PSPW index, intercellular spaces, and pathophysiological characteristics among PPI responsive NERD patients, PPI non-responsive NERD patients and FH patients. We also evaluated the efficacy of MNBI and PSPW index in discriminating NERD from FH patients and NERD/PPI responders from NERD/PPI nonresponders. This study aims to evaluate

the effect of measuring MNBI and PSPW index in identifying PPI-refractory NERD patients.

Materials and Methods

Study Subjects

We analyzed consecutive subjects referred to our outpatient clinics between Jan 2014 and Jan 2018 whose endoscopic testing showed no evidence of erosion within 1 week before undergoing MII-pH monitoring. Patients over 18 years old with symptoms of heartburn and/or regurgitation persisting for more than 6 months and score of validated Reflux Disease Questionnaire no less than 12 were included.¹⁷ NERD patients were treated with rabeprazole or omeprazole 20 mg per day for at least 8 weeks. They were considered as NERD/PPI nonresponders when the improvement of symptom score was less than 50.0%,¹⁸ while classified as NERD/PPI responders if improvement \geq 50.0%. Patients were excluded if they had peptic stricture or ulcer, history of tumor or surgery, and severe esophageal motility disorders. The Ethical Committee of the hospital approved this study (IRB No. 2014-SR-010). All subjects gave standard informed written consent before commencement of this study.

Esophageal Multichannel Intraluminal Impedance and pH Monitoring

Subjects were asked to stop PPIs or prokinetic drug medication at least 2 weeks before the MII-pH monitoring. The MII-pH catheter (Given Imaging) was positioned by an experienced nurse and then inserted into the esophagus and taped to the face. The pH sensor was located at 5 cm proximal to lower esophageal sphincter (LES) and the z1 to z6 impedance probes were at 17, 15, 9, 7, 5, and 3 cm proximal to the LES, respectively.¹⁹ All subjects were instructed to record the activities, symptoms, meals, and time of the supine posture during the 24 hours of measurement.

Multichannel Intraluminal Impedance and pH Data Analysis

We measured and calculated the following variables: (1) numbers and types of reflux episodes;²⁰ (2) DeMeester score; (3) acid exposure time (AET); (4) MNBI values; and (5) PSPW index. Reflux episodes were divided into acidic (pH < 4.0), weakly acidic (pH 4.0-7.0), and weakly alkaline (pH > 7.0) refluxes.²¹ AET was calculated as the time of pH below 4 at the distal esophagus, divided by the total time of testing. Patients were classified as NERD if

Table 1. Baseline Characteristics of Patients With Non-erosive Reflux Disease and Functional Heartburn

Characteristics	Total NERD (n = 50)	FH (n = 20)	NERD/PPI responders (n = 25)	NERD/PPI non-responders (n = 25)
Age (yr)	51.6 ± 14.0	56.3 ± 13.1	53.2 ± 12.9	50.1 ± 15.1
Male	27 (54)	9 (45)	14 (56)	13 (52)
DeMeester score	19.9 ± 11.9	6.0 ± 4.7 ^a	24.0 ± 6.2	15.7 ± 14.7 ^b
AET (%)	5.7 ± 3.4	1.7 ± 1.3 ^a	6.9 ± 1.8	4.5 ± 4.2 ^b
Acid refluxes	77.5 (44.3, 113.5)	20.0 (6.0, 39.0) ^a	100.0 (67.5, 146.0)	63.0 (28.0, 83.0) ^b
Weakly acid refluxes	19.0 (10.0, 37.3)	10.5 (6.0, 12.0) ^a	13.0 (5.0, 26.0)	26.0 (15.0, 54.0) ^c
Weakly alkaline refluxes	2.0 (1.0, 5.8)	0 (0, 0) ^a	1.0 (1.0, 3.0)	3.0 (1.5, 13.0)
Long term acid (> 5 min)	3.0 (1.0, 5.0)	1.0 (0, 1.5) ^a	4.0 (2.0, 7.0)	1.0 (1.0, 5.0) ^b

NERD, non-erosive reflux disease; FH, functional heartburn; PPI, proton pump inhibitor; AET, acid exposure time.

^aP-value < 0.001 compared with total NERD.

^bP-value < 0.05 compared with NERD/PPI responders.

^cP-value < 0.01 compared with NERD/PPI responders.

Data are presented as mean ± standard deviation, n (%), or median (interquartile range: 25th, 75th).

AET > 4.0% and/or reflux episodes > 80, while FH was defined by normal AET, reflux episodes, and symptom association analysis.³

Baseline impedance levels were assessed blindly by 1 investigator who was unaware of the diagnostic results at three 10-minute time periods around 1 AM, 2 AM, and 3 AM, which were not close to any periods of swallows, refluxes, and pH drops.²² MNBI was the average value of 3 appropriate baseline impedance levels from each time period. MNBI from the impedance channel z5 was chosen for analysis, at which the pH sensor located to ensure that MNBI were obtained when pH > 6.²³ The definition of PSPW was an antegrade 50.0% drop occurring within 30 seconds after a reflux event, originating from the most proximal impedance channel to all remaining distal impedance channels, and followed by at least 50.0% return to the baseline. The PSPW index was measured when dividing the number of PSPWs by the total reflux events.¹³

Transmission Electron Microscopy Examination

The biopsy specimens from endoscopy were obtained at the site within 3 cm proximal to the esophagogastric junction.²⁴ The samples were fixed in a 2.5% glutaraldehyde solution at 4°C and then post-fixed in 1.0% osmium tetroxide, infiltrated in Epon's resin, embedded and sectioned into ultra-thin slices.¹⁰ The specimens were observed and photographed under transmission electron microscopy (Hitachi, Tokyo, Japan). Intercellular spaces of the esophageal epithelial cells were evaluated using image analyzing system (Leica, Wetzlar, Germany). Ten pictures were obtained from each slice. Each image contained an intact cell and the vertical distance between the intact cell and its neighboring cells in 10 random directions was used to evaluate the intercellular space. In total, 100 intercellular spaces from 10 images were marked. The average

value of intercellular space was calculated by an investigator who was unaware of the endoscopy and MII-pH findings.

Statistical Methods

Continuous parameters were presented as mean ± standard deviation or median (interquartile range: 25th, 75th). Data were compared using unpaired Student's *t* test if found to follow a normal distribution and Mann-Whitney *U* test if not. Categorical data were presented as frequencies and proportions and compared using the chi-square test or Fisher's exact test. The correlation between MNBI and AET as well as PSPW index were investigated using Pearson's correlation statistics. The predictive values of MNBI, PSPW index and AET distinguishing NERD from FH patients were estimated using receiver operating characteristic (ROC) curves. Differences were considered statistically significant when *P* value < 0.05.

Results

Patient Characteristics

In total, we enrolled 50 NERD patients, including 25 NERD/PPI responders and 25 NERD/PPI nonresponders, and 20 FH patients. Patient demographic and clinical characteristics are reported in Table 1. Compared to patients with FH, the AET, DeMeester score, and reflux events were significantly higher in the NERD group. On the basis of response to PPI, the AET, DeMeester score, and episodes of acid, weakly acid, long term acid reflux (> 5 minutes) were higher in NERD/PPI responders than in NERD/PPI nonresponders, while episodes of weakly alkaline

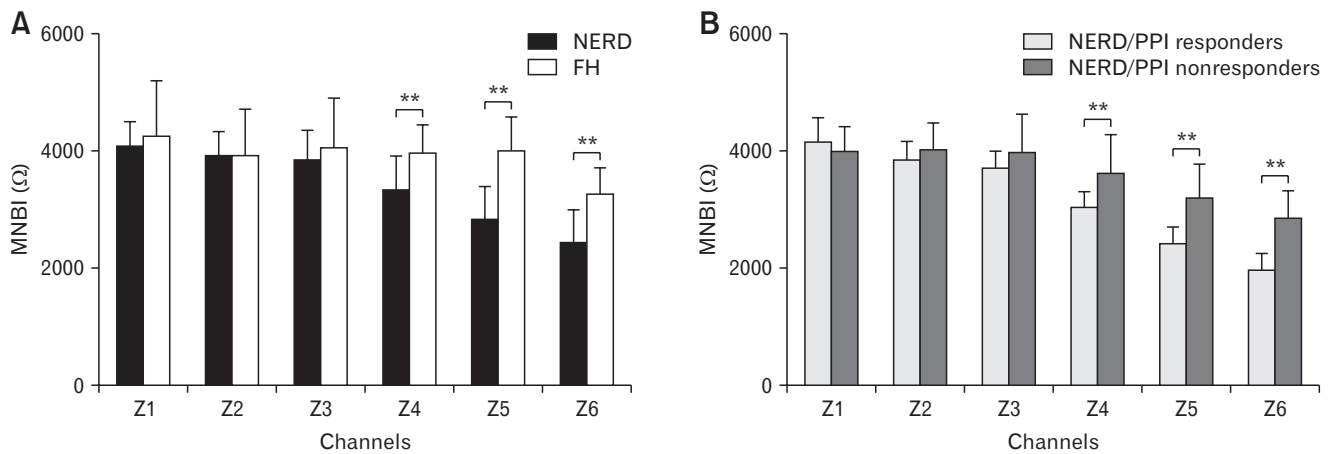


Figure 1. Mean nocturnal baseline impedance (MNBI) levels from each impedance channel in: (A) non-erosive reflux disease (NERD) and functional heartburn (FH) patients and (B) NERD/proton pump inhibitor (PPI) responders and NERD/PPI nonresponders. ** $P < 0.01$.

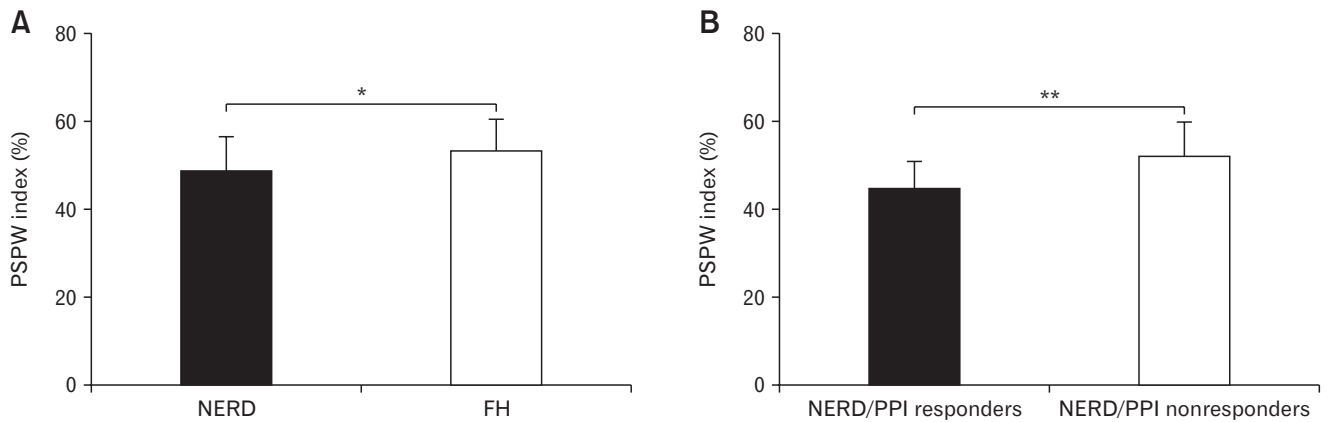


Figure 2. Comparison of post-reflux swallow-induced peristaltic wave (PSPW) index between: (A) non-erosive reflux disease (NERD) and functional heartburn (FH) patients and (B) NERD/proton pump inhibitor (PPI) responders and NERD/PPI nonresponders. * $P < 0.05$, ** $P < 0.01$.

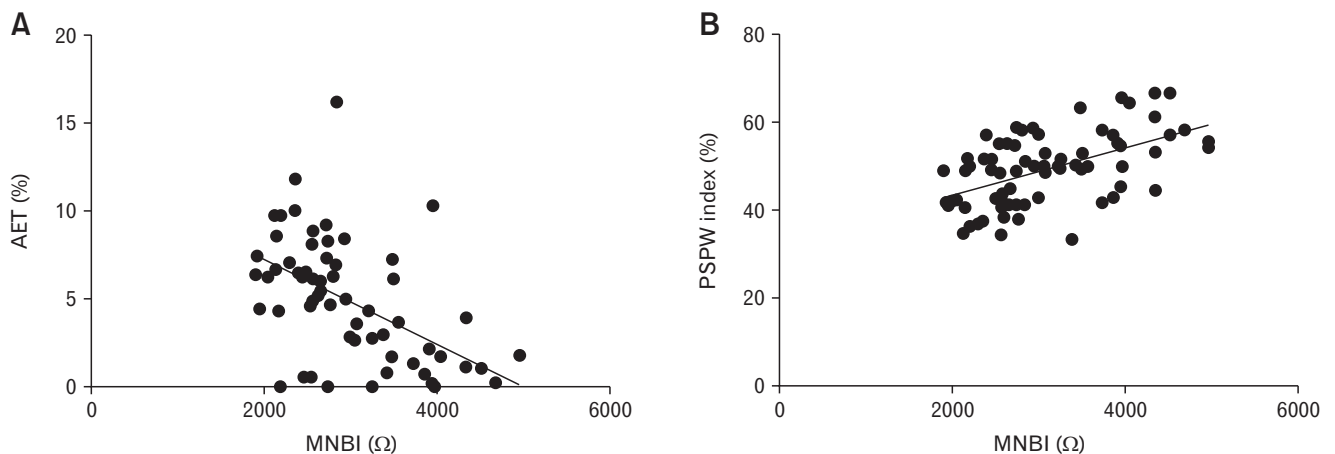


Figure 3. Correlation between mean nocturnal baseline impedance (MNBI) levels (z5) and: (A) acid exposure time (AET), (B) post-reflux swallow-induced peristaltic wave (PSPW) index. AET, acid exposure time.

reflux demonstrated no significant differences between them.

Mean Nocturnal Baseline Impedance and Post-reflux Swallow-induced Peristaltic Wave Analysis

MNBI values from each channel across groups are shown in Figure 1. MNBI from z4, z5, and z6 in total NERD patients were significantly lower compared to FH patients (3299.8 ± 605.7 vs $3926.5 \pm 511.0 \Omega$, $P < 0.001$; 2782.8 ± 606.9 vs $3974.0 \pm 598.4 \Omega$, $P < 0.001$; 2384.9 ± 602.6 vs $3232.9 \pm 469.9 \Omega$, $P < 0.001$, respectively). Similarly, the lower MNBI values from z4 to z6 in NERD/PPI responders were observed compared to NERD/PPI nonresponders (3005.6 ± 302.9 vs $3594.1 \pm 690.5 \Omega$, $P < 0.001$; 2394.0 ± 293.2 vs $3171.5 \pm 592.6 \Omega$, $P < 0.001$; 1940.0 ± 294.4 vs $2829.8 \pm 492.3 \Omega$, $P < 0.001$, respectively).

PSPW index was significantly lower in the total NERD group

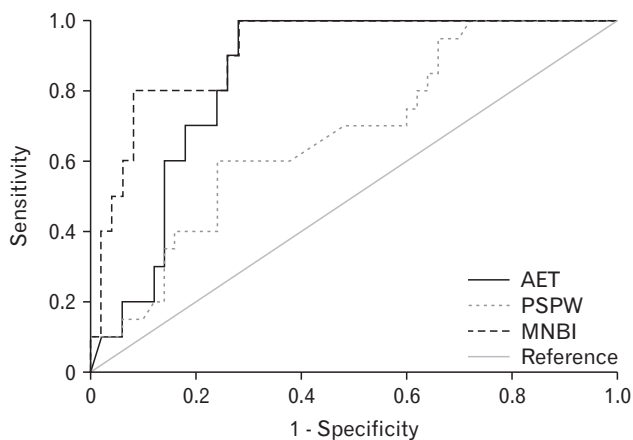


Figure 4. Receiver operating characteristic (ROC) curves for distinguishing functional heartburn (FH) from non-erosive reflux disease (NERD) patients. AET, acid exposure time; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance.

compared to FH group ($48.2 \pm 8.1\%$ vs $53.0 \pm 7.4\%$, $P = 0.024$). NERD/PPI responders had lower PSPW index compared to NERD/PPI nonresponders ($44.5 \pm 6.5\%$ vs $51.9 \pm 8.0\%$, $P = 0.001$) (Fig. 2).

We found significant correlation between MNBI and acid exposure as well as chemical clearance. Distal esophageal MNBIs negatively correlated with AET ($r = -0.552$, $P < 0.001$) while positively correlated with PSPW index ($r = 0.525$, $P < 0.001$) (Fig. 3).

The Diagnostic Efficacy of Mean Nocturnal Baseline Impedance and Post-reflux Swallow-induced Peristaltic Wave

For distinguishing NERD from FH patients, ROC analysis was performed (Fig. 4) with areas under the curve (AUC) of 0.677, 0.843, and 0.914 for PSPW index, AET, and MNBI (Table 2). Cutoff values of PSPW index, AET, and MNBI were 52.9%, 4.2%, and 3562.0 Ω , respectively. We also explored the ability of the 3 impedance parameters in discriminating NERD PPI/respond-

Table 2. Diagnostic Accuracy of Impedance Parameters in Patients With Non-erosive Reflux Disease and Functional Heartburn

Items	AET (%)	PSPW index (%)	MNBI (Ω)
AUC	0.843	0.677	0.914
95% CI	0.753-0.933	0.544-0.810	0.848-0.980
P-value	< 0.01	0.021	< 0.01
Cutoff value	4.2	52.9	3562.0
Sensitivity (%)	72.0	60.0	92.0
Specificity (%)	100.0	76.0	80.0
PPV (%)	100.0	82.6	92.0
NPV (%)	58.8	50.0	80.0

AET, acid exposure time; PSPW, post-reflux swallow-induced peristaltic wave; MNBI, mean nocturnal baseline impedance; AUC, areas under the curve; PPV, positive predictive value; NPV, negative predictive value.

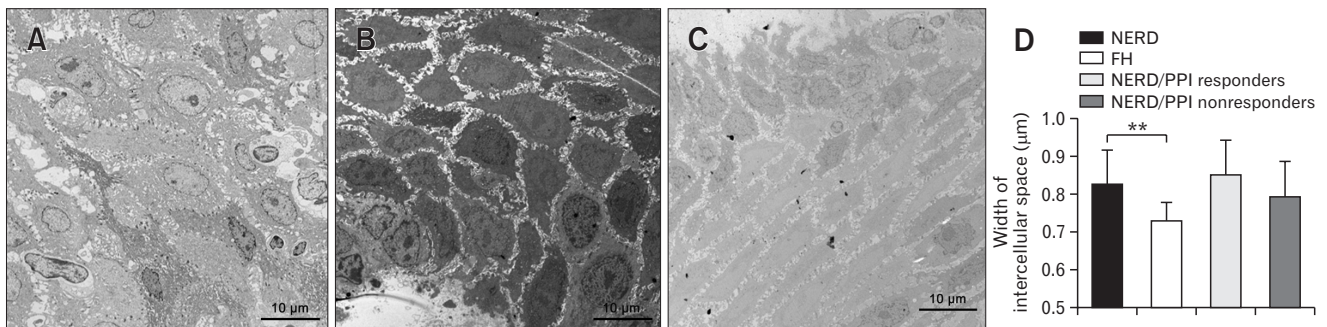


Figure 5. Comparison of the width of intercellular space among (A) functional heartburn (FH), (B) non-erosive reflux disease (NERD)/proton pump inhibitor (PPI) responders, (C) NERD/PPI nonresponders, and width of intercellular spaces in all groups (D). ****** $P < 0.01$.

ers from NERD PPI/nonresponders. AET, PSPW index, and MNBI yielded AUC of 0.727, 0.774, and 0.893 with cutoff values of 4.4%, 49.1%, and 2729.3 Ω ($P = 0.006$, $P = 0.001$, $P < 0.001$, respectively). The sensitivity, specificity, positive and negative predictive values for evaluating PPI response in NERD patients were as follows: AET, 60.0%, 96.0%, 94.0%, and 71.0%; PSPW index, 80.0%, 76.0%, 77.0%, and 79.0%; MNBI, 80.0%, 92.0%, 91.0%, and 82.0% respectively.

Intercellular Spaces in the Esophageal Epithelium of Patients

All patients showed ultrastructural integrity of the esophageal epithelial cells. The width of intercellular spaces of the NERD group were greater than that of FH (NERD vs FH: $0.82 \pm 0.02 \mu\text{m}$ vs $0.73 \pm 0.02 \mu\text{m}$, $P = 0.005$), but there was no difference between NERD/PPI responders and nonresponders ($0.85 \pm 0.03 \mu\text{m}$ vs $0.80 \pm 0.03 \mu\text{m}$, $P = 0.108$) (Fig. 5).

Discussion

In this study, we investigated the clinical value of MNBI and PSPW index in patients with NERD and FH. We demonstrated that MNBI correlated to acid exposure and chemical clearance. Specifically, we determined that MNBI and PSPW index could discriminate between NERD and FH patients as well as NERD/PPI responders and NERD/PPI nonresponders.

Currently, MII-pH monitoring is frequently used to estimate whether pathologic reflux exists and whether symptoms are associated with reflux events in patients with negative endoscopic results. Novel impedance metrics including PSPW index and MNBI have been proposed to evaluate esophageal chemical clearance and mucosal integrity. Kandulski et al¹¹ demonstrated that distal baseline impedance could distinguish GERD from FH patients with the cutoff value, sensitivity, and specificity of 2100 Ω , 78.0%, and 71.0%, respectively. Furthermore, Xie et al²⁴ reported 1764 Ω as the cutoff value of baseline impedance to differentiate patients with GERD from healthy subjects with 55.4% sensitivity and 100.0% specificity in the Chinese population. The cutoff value of MNBI to separate NERD from FH patients in our study is 3562 Ω , which is a high level compared to previous study. This is probably because we chose metrics from the channel located 5 cm above the LES to perform ROC analysis and we did not include patients who had erosive reflux disease in this study. MNBI reflects esophageal mucosal integrity²⁵ and PSPW could be elicited by both acidic and weakly acidic refluxes.¹³ In this study, both MNBI and PSPW

index could separate NERD from FH patients, and MNBI may be more efficient than PSPW index. Considering the day-to-day variability presented by AET,²⁶ MNBI and PSPW index may be reliable parameters to distinguish GERD phenotypes when conventional MII-pH metrics afford ambiguous results.

We found that MNBI and PSPW index were also associated with PPI response in patients with NERD. NERD/PPI responders showed lower MNBI levels and PSPW index than NERD/PPI nonresponders. At ROC analysis, both metrics showed high efficacy in differentiating between NERD/PPI responders and nonresponders. This was supported by the finding that the acid exposure was more severe in PPI responsive NERD patients. Previously, MNBI and PSPW index linked reflux with PPI-effectiveness better than AET.²⁷ Low PSPW index reflects impairment of chemical clearance and implies prolonged contact of mucosa with refluxes, which further leads to esophageal mucosal damage despite adequate acid suppression.^{13,28} Given the fact that patients with NERD respond less favorably to PPIs, MNBI, and PSPW index may be ideal markers to predict the efficacy of PPI in NERD patients.

GERD results from acid exposure, which affects mucosal integrity and further results in dilated intercellular spaces (DIS) and increased paracellular permeability in the epithelium.¹⁰ A previous study suggested that DIS may occur even when no visible mucosal damage could be observed at endoscopy²⁹ and is typically present in patients with NERD.¹⁰ We showed that the width of intercellular spaces of the NERD group were greater than that of FH, indicating that DIS has the potential to segregate NERD from FH. We found no difference of the dilation of intercellular spaces between NERD PPI/responders and NERD PPI/nonresponders, which is consistent with a previous report.²⁴ This is probably because DIS also results from inflammation other than acid exposure.

One of the limitations in this study is that we lack healthy subjects as a control group, which limits the association of MNBI and PSPW index with specific symptoms and endoscopic characteristics. Furthermore, we did not include patients with reflux hypersensitivity. We aimed to explore the relationship between MNBI or PSPW and pathological reflux in this study. Gao et al³⁰ found that patients with reflux hypersensitivity showed lower PSPW index and MNBI values than FH patients and healthy volunteers. The immune reaction induced by the visceral hypersensitivity may cause DIS in patients without mucosal erosion. In fact, the inclusion of patients with hypersensitive esophagus would be helpful to explore the role of MNBI and PSPW index in different phenotypes of endoscopy-negative patients. In addition, the retrospective review of

impedance-pH tracings may lead to misclassification of endoscopy negative patients if some did not stop PPI before the endoscopy.

In summary, this study evaluated the clinical utility of MNBI and PSPW index in patients with negative endoscopy. MNBI and PSPW index resulted to be useful in identifying patients with NERD from patients with FH. In addition, the efficacy of MNBI and PSPW index to identify PPI responsive NERD patients is acceptable. MNBI and PSPW index may be a promising metric to guide diagnosis and management in patients with NERD.

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Conflicts of interest: None.

Author contributions: Yan Wang, Bixing Ye, Lin Lin, and Linqin Jiang conceived and designed the experiments; Bixing Ye, Linqin Jiang, and Meifeng Wang performed the experiments; Yan Wang, Bixing Ye, and Linqin Jiang analyzed the data; and Yan Wang and Liuqin Jiang wrote the manuscript.

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