



Mean Nocturnal Baseline Impedance and Post-reflux Swallow-induced Peristaltic Wave Index Could Identify Gastroesophageal Reflux Disease but pH-Impedance Metrics Alone Might Not Correlate With Proton Pump Inhibitor Response in Chinese Patients With Typical Reflux Symptoms

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Background/Aims

Lyon consensus differentiates acid exposure time (AET) as physiological, borderline, and pathological. Mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave index (PSPWi) are believed to increase diagnostic yield of gastroesophageal reflux disease (GERD) and correlate with symptom outcome of proton pump inhibitor (PPI) treatment. We aim to explore the clinical characteristics and the correlation of pH-impedance parameters with PPI response in Chinese patients with different AET levels.

Methods

We retrospectively investigated 177 patients with typical reflux symptoms who received esophageal function tests. The demographics, GERD questionnaire scores, the proportion of esophagitis and PPI responders, and manometric and pH-impedance parameters were compared among patients with AET < 4%, 4-6%, and > 6%. In patients with AET ≥ 4%, manometric and pH-impedance parameters were compared between PPI responders and non-responders.

Results

Among 177 patients, 69 (39.0%) had AET 4-6%, and 53 (29.9%) had AET > 6%. The demographics, esophagogastric junction type, and occurrence of ineffective esophageal motility were similar between patients with AET 4-6% and > 6%, but different from AET < 4%. MNBI and PSPWi were different among different AET levels, but similar between PPI responders and non-responders in patients with AET ≥ 4%.

Conclusions

It is reasonable to set 4% as a threshold to define pathological AET in Chinese patients. MNBI and PSPWi could identify GERD patients, but may not correlate with PPI response of Chinese GERD patients.

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Key Words

Electric impedance; Gastroesophageal reflux; Proton pump inhibitors

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Introduction

In clinical practice, ambulatory reflux monitoring can provide confirmatory evidence of gastroesophageal reflux disease (GERD).¹ Acid exposure time (AET) is the most consistent predictor of acid reflux burden.² According to the Lyon consensus, AET less than 4% was physiologic and greater than 6% was pathologic, while AET between 4% and 6% was classified as borderline or inconclusive.³ However, recently, the 2020 Seoul consensus of the management of GERD which mainly focuses on the Asian population defined pathologic acid reflux when $AET \geq 4\%$.⁴ The reason for the threshold change was mainly based on a meta-analysis of the AET of asymptomatic Asians from 19 studies in which the 95% CI of the AET was 2.7-3.9%. Besides, 2 studies from China (with 28 and 38 patients with AET between 4-6% respectively, and 47 and 113 patients of AET > 6% respectively) displayed the manometric and pH-impedance characteristics of the 2 groups of patients were similar.^{5,6} More data of the Chinese patients especially with a larger sample size of the patients with AET between 4-6% are preferred to evaluate whether the threshold of AET set as 4% is reasonable.

Twenty-four hour esophageal multichannel intraluminal impedance and pH monitoring (24-hour pH-MII) provides more information than acid exposure. With impedance, reflux could be differentiated as acid, weakly acid, and alkaline reflux. Moreover, novel parameters, mean nocturnal baseline impedance (MNBI) could reflect esophageal mucosal barrier integrity, and post-reflux swallow-induced peristaltic wave index (PSPWi) can reflect the ability of chemical clearance. It was demonstrated that in patients with typical reflux symptoms, MNBI was lower in patients with both AET between 4-6% and > 6% than patients with AET < 4%,^{5,7} and the same trend was found in Chinese patients with low-grade esophagitis.⁸ Low MNBI (MNBI < 2292 Ω) is believed as a good supportive evidence of GERD diagnosis.^{7,9} Studies

from Western populations demonstrated that in patients with typical reflux symptoms, low MNBI was found in about 99.0% of patients with AET > 6%, about 91.0% of patients with AET between 4-6%, and about 33% of patients with AET < 4%.⁷ In patients with suspected GERD-related extraesophageal patients, low MNBI was found in about 88.0% of true GERD patients and 12.0% of non-GERD patients (identified with 24-hour pH-MII).¹⁰ The percentages of low MNBI in Chinese patients with different AET levels are not known. Likewise, accumulating data demonstrated the ability of PSPWi to differentiate GERD from non-GERD. It was found that PSPWi was about 25.0-30.0% in patients with non-erosive reflux disease, 15.0-25.0% in patients with esophagitis, and 45.0-76.0% in patients with functional heartburn.¹¹⁻¹³ There is a study from China that demonstrated that the mean PSPWi of patients with AET > 6%, between 4-6% and > 6% were 59.8%, 78.6%, and 84.1%, respectively.⁵ The PSPWi in this study seems higher than previous studies, and more data of the PSPWi in different AET levels is needed.

Besides identifying GERD, the predictive ability of both MNBI and PSPWi for anti-reflux treatment response had been shown in patients with typical reflux symptoms,¹⁴⁻¹⁶ with AET between 4-6%,⁷ and with extra-esophageal reflux symptoms.¹⁰ However, recently, a study from China demonstrated that in patients with AET 4-6%, the proton pump inhibitor (PPI) response rates were not different between patients with normal MNBI and low MNBI.⁶ It is worth knowing the correlation of MNBI and PSPWi with PPI response in Chinese patients with different AET levels.

In this study, we aim to analyze the symptomatic, endoscopic, manometric and pH-impedance characteristics of patients with different AET levels to determine whether the AET threshold set at 4% is reasonable to define abnormal acid exposure. Moreover, we aim to evaluate the correlation of MNBI, PSPWi, and AET with PPI response in Chinese GERD patients with typical reflux symptoms.

Materials and Methods

Participants and Study Design

Patients who suffered typical reflux symptoms and received high-resolution manometry and 24-hour pH-MII in Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from May 2011 to May 2020 were included in this retrospective study. These patients accepted esophageal function tests because they had refractory GERD symptoms for at least 8 weeks of the standard dose of PPI or they wanted by themselves to know whether they had excessive acid exposure before PPI treatment, or they were PPI responders who wanted to get anti-reflux endoscopic or surgical procedure. Patients with Grade C and D esophagitis defined by Los Angeles classification, long-segment Barrett mucosa, peptic esophageal stricture, and patients with extra-esophageal symptoms were excluded.¹²

Patients were categorized as 3 groups: physiologic group (AET < 4%), inconclusive group ($4\% \leq \text{AET} \leq 6\%$), and pathologic group (AET > 6%).³ Demographics, symptoms, PPI response, endoscopic reports, high-resolution manometry, and 24-hour pH-MII monitoring parameters were all collected and compared among different AET groups.

The protocol of this study was approved by The Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology and registered at <http://www.chictr.org.cn> (No. ChiCTR2100042688).

Demographics and Clinical Characteristics

Demographics include age, gender, body mass index, smoking, and drinking. GERD questionnaire (GerdQ) is a questionnaire for the diagnosis of GERD based on the typical and troublesome symptoms of GERD, such as regurgitation and heartburn.¹⁷ Diagnosis of esophagitis by endoscopy was defined by the Los Angeles classification,¹⁸ and the endoscopy was done within 14 days before high-resolution esophageal manometry and 24-hour pH-MII monitoring. PPI response was positive when patients' symptoms improved by more than 50.0% compared with the baseline, and PPI non-responder definition was based on the symptom outcome of at least 8 weeks of the standard dose of PPIs. Symptom outcomes were collected in clinical records or from interviews by phone calls.

High-resolution Esophageal Manometry

High-resolution esophageal manometry (HREM) was performed by using a solid-state (Sierra Scientific Instruments, Inc, Los Angeles, CA, USA) or a water perfusion catheter (Solar GI HRM, Medical Measurement System, Enschede, The Netherlands). The data analysis was performed by 2 experienced investigators. We collected the parameters such as the type of esophagogastric junction (EGJ) morphology (EGJ I, II, or III), low esophageal sphincter (LES) pressure based on the Chicago classification version 3.0.¹⁹ Hypotensive EGJ was defined when LES pressure was < 10 mmHg. If the frequency of the ineffective swallow reached 50.0% out of water swallows, ineffective esophageal motility (IEM) was diagnosed.¹⁹

Twenty-four-hour Esophageal pH-Impedance Monitoring

Participants with a history of PPI use needed to stop using the PPI for at least 1 week before the 24-hour pH-impedance monitoring test. The pH-impedance measurement was performed with a catheter containing 1 pH channel and 6 impedance channels (Given Imaging, Inc, Mansfield, MA, USA). Patients were instructed to record the time of the positions (upright or supine), meals, and symptoms occurring in the diary. Two experienced investigators analyzed the data by using the Accuview pH-Z version 5.2 software (Given Imaging, Inc).

A fall of pH below 4 at 5 cm above LES was taken to indicate acid reflux, and acid reflux episodes were divided into upright and supine episodes.³ Long reflux was defined as the duration of pH < 4 reaching 5 minutes. AET was the percentage of the total time of pH < 4 in 24 hours. MNBI, from 3 cm above LES, was calculated by manual measurement of mean baseline values at 3 different 10-minute periods (around 1 AM, 2 AM, and 3 AM), excluding reflux episodes and swallows.²⁰ 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 (PSPWi) was obtained when dividing the number of PSPWs by the number of reflux events.²¹ The cutoff for the definition of low MNBI and PSPWi were 2292 Ω and 61.0% respectively.⁷ Symptom association probability (SAP) index was calculated according to described criteria.²² Reflux episodes include acidic reflux, weakly acidic reflux, and alkaline reflux. A total reflux number > 80 and SAP > 95.0% were positive.⁷

Table 1. Demographics, Symptoms, and Symptom Outcome of All Participants

Characteristics	Total (N = 177)	AET < 4% (n = 55)	4% ≤ AET ≤ 6% (n = 69)	AET > 6% (n = 53)	P-value	AET ≥ 4% (n = 122)	P-value
Demographics							
Age (yr)	49.8 ± 11.5	46.5 ± 10.4	52.1 ± 11.9 ^a	50.3 ± 11.4	0.023	51.3 ± 11.7	0.009
Male	100 (56.5)	23 (41.8)	39 (56.5)	38 (71.7) ^b	0.007	77 (63.1)	0.008
BMI (kg/m ²)	22.8 ± 3.3	22.0 ± 3.8	23.3 ± 3.0	23.0 ± 3.0	0.070	23.2 ± 3.0	0.024
Smoking	36 (20.3)	11 (20.0)	9 (13.0)	16 (30.2)	0.066	25 (20.5)	0.940
Drinking	30 (17.0)	9 (16.4)	12 (17.4)	9 (17.0)	0.989	21 (17.2)	0.889
Symptoms							
GerdQ (total)	8.2 ± 2.5	7.9 ± 2.6	7.9 ± 2.4	8.8 ± 2.4	0.104	8.3 ± 2.4	0.352
GerdQ (NERD)	8.1 ± 2.4	7.9 ± 2.7	7.9 ± 2.2	8.6 ± 2.4	0.317	8.2 ± 2.3	0.569
Symptom outcome							
PPI response	107 (60.5)	20 (36.4)	48 (69.6) ^a	39 (73.6) ^b	< 0.001	87 (71.3)	< 0.001

^aP < 0.05 for acid exposure time (AET) < 4% and 4% ≤ AET ≤ 6%.

^bP < 0.05 for AET < 4% and AET > 6%.

BMI, body mass index; GerdQ, gastroesophageal reflux disease questionnaire; NERD, non-erosive reflux disease; PPI, proton pump inhibitor. Data are presented as mean ± SD or n (%).

Table 2. Comparison of Endoscopic, Manometric, and pH-Impedance Parameters of All Participants

Parameters	Total (N = 177)	AET < 4% (n = 55)	4% ≤ AET ≤ 6% (n = 69)	AET > 6% (n = 53)	P-value	AET ≥ 4% (n = 122)	P-value
Endoscopy							
Esophagitis	39 (22.0)	8 (14.6)	15 (21.7)	16 (30.2)	0.146	31 (25.4)	0.107
Grade A	17 (9.6)	6 (10.9)	5 (7.3)	6 (11.3)	-	11 (9.0)	-
Grade B	22 (12.4)	2 (3.6)	10 (14.5)	10 (18.9)	-	20 (16.4)	-
24-Hour pH-impedance parameters							
MNBI (Ω)	2740 ± 1377	4053 ± 1031	2471 ± 1085 ^{a,b}	1725 ± 840 ^c	< 0.001	2147 ± 1050	< 0.001
MNBI < 2292	75 (42.4)	2 (3.6)	31 (44.9) ^{a,b}	42 (79.3) ^c	< 0.001	73 (59.8)	< 0.001
PSPWi (%)	29.4 ± 20.1	46.2 ± 23.2	26.4 ± 12.2 ^{a,b}	16.0 ± 10.9 ^c	< 0.001	21.9 ± 12.7	< 0.001
PSPWi < 61%	150 (84.7)	31 (56.4)	67 (97.1) ^a	52 (98.1) ^c	< 0.001	119 (97.5)	< 0.001
Reflux episodes	41.4 ± 31.2	37.1 ± 28.0	39.5 ± 25.7	48.5 ± 39.1	0.131	43.4 ± 32.4	0.210
Weakly acidic reflux	21.6 ± 21.7	25.9 ± 19.8	18.4 ± 18.1	21.3 ± 26.9	0.161	19.7 ± 22.3	0.077
Alkaline reflux	0.8 ± 2.6	1.4 ± 3.5	0.7 ± 2.3	0.4 ± 1.5	0.118	0.6 ± 2.0	0.106
Reflux episodes > 80	12 (6.8)	1 (1.8)	4 (5.8)	7 (13.2) ^c	0.057	11 (9.0)	0.108
SAP > 95%	64 (36.2)	18 (32.7)	21 (30.4)	25 (47.2)	0.132	46 (37.7)	0.524
HRM parameters							
EGJ II/III	41 (23.2)	5 (9.1)	18 (26.1) ^a	18 (34.0) ^c	0.007	36 (29.5)	0.003
Hypotensive EGJ	57 (32.2)	14 (25.5)	28 (40.6)	15 (28.3)	0.155	43 (35.3)	0.197
IEM	96 (54.2)	22 (40.0)	42 (60.9) ^a	32 (60.4) ^c	0.038	74 (60.7)	0.011

^aP < 0.05 for acid exposure time (AET) < 4% and 4% ≤ AET ≤ 6%.

^bP < 0.05 for AET > 6% and 4% ≤ AET ≤ 6%.

^cP < 0.05 for AET < 4% and AET > 6%.

MNBI, mean nocturnal baseline impedance; PSPWi, post-reflux swallow-induced peristaltic wave index; SAP, symptom association probability; HRM, high-resolution manometry; EGJ, esophagogastric junction; IEM, ineffective esophageal motility. Data are presented as n (%) or mean ± SD.

Statistical Methods

All statistical analysis was performed using SPSS statistics 25.0 (IBM, Armonk, NY, USA). The continuous data were described by the mean and standard deviation (mean \pm SD), and the distribution of the categorical data was expressed as a percentage (%). Pearson correlation coefficient analysis was used for correlation analysis. Continuous data were compared using the *t* test or ANOVA test, and categorical data were compared using the chi-squared test. Games-Howell test was used for the post hoc test. The significance level (*P*-value) with 2-tails was set at 0.05.

Results

Demographic, Symptoms, and Proton Pump Inhibitor Response of Patients With Different Acid Exposure Time Levels

A total of 177 eligible patients were included in this study. There were 55 patients with AET < 4%, 69 with AET 4-6%, and 53 with AET > 6%. Patients with AET 4-6% and > 6% were with similar in terms of age, gender ratio, body mass index, and habits of smoking and drinking. In patients with AET < 4%, there were more females and more patients with younger age and lower body mass index (Table 1).

GerdQ scores of patients with AET < 4%, 4-6%, and > 6% were similar (Table 1). Proportions of PPI response were similar between patients with AET > 6% and AET between 4-6% (*P* =

0.627), but were both significantly higher than patients with AET < 4% (both *P* < 0.05).

Endoscopic, Manometric, and pH-Impedance Parameters of Patients With Different Acid Exposure Time Levels

In patients with esophagitis, they are all grade A or grade B. As shown in Table 2, about 14.6% of patients with AET < 4%, 21.7% of patients with AET 4-6%, and 30.2% of patients with AET > 6% were with esophagitis, and the proportions of esophagitis of patients with AET 4-6% and > 6% seemed higher than patients with AET < 4% from the perspective of the exact value, but it did not reach statistical significance. However, in patients with esophagitis whose AET was \geq 4%, the proportion of grade B esophagitis was higher in patients with esophagitis whose AET was < 4% (64.5% vs 25.0%, *P* = 0.044). This means that the esophagitis of patients with AET \geq 4% was more severe because they were grade B predominant, and patients with AET < 4% were grade A predominant.

The proportions of type II/III EGJ and IEM were similar between patients with AET between 4-6% and > 6%, but they were higher than patients with AET < 4%.

Of 177 patients, MNBI and PSPWi were associated with AET numerically (Pearson's *r* = -0.403, -0.324, both *P* < 0.001). There were significant differences in MNBI and PSPWi among patients in 3 AET groups. The patients with AET > 6% had the lowest MNBI and PSPWi, and patients with AET < 4% had the highest MNBI and PSPWi. More than 97% of the patients with AET \geq 4% were with PSPWi < 61.0%, and 56.4% of the pa-

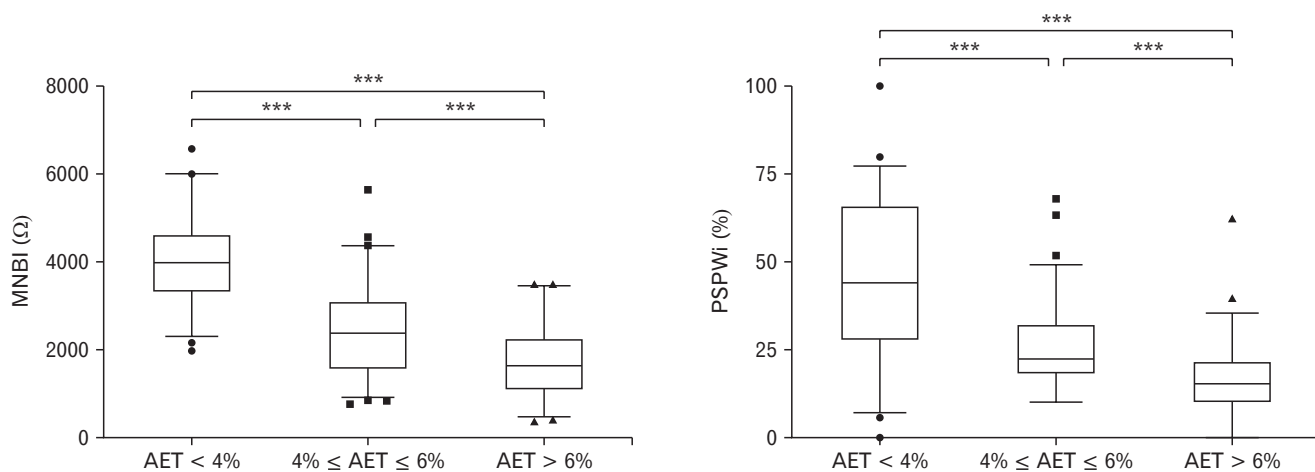


Figure. Mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave index (PSPWi) of patients with different acid exposure time (AET). The extents of the box plots represent 25th–50th–75th percentile values, and the whiskers depict 5th and 95th percentile values. Squares, circles, and triangles represent outlier values. ****P* < 0.001 in post hoc analysis of ANOVA test among 3 groups.

tients with AET < 4% were with PSPWi < 61.0%. About 59.8% of the patients with AET ≥ 4% were with MNBI < 2292 Ω, and only 3.6% of the patients with AET < 4% were with MNBI < 2292 Ω. (all $P < 0.001$) (Table 2 and Figure) The reflux episodes, weakly acidic reflux, alkaline reflux, and SAP were similar among the 3 AET groups.

Correlation of Manometric and pH-Impedance Parameters and Proton Pump Inhibitor Response in Patients With Acid Exposure Time ≥ 4%

Comparison of 24-hour pH-impedance and HREM parameters between PPI responders and non-responders of patients with AET ≥ 4% are summarized in Table 3. No statistical significance was found for the manometric and pH-impedance parameters between PPI-responders and non-responders. We compared again in patients with non-erosive reflux disease, and still no statistical significance could be found (Table 3).

Discussion

In this study, using data collected from 177 patients with typical reflux symptoms, we show that the reflux symptoms, proportion of esophagitis, type II/III EGJ, IEM, and PPI response between patients with AET 4-6% and AET > 6% are comparable, and most

of the items of the 2 groups are different from patients with AET < 4%. With regards to the pH-impedance parameters, the total reflux episodes, weakly acid reflux episodes, alkaline reflux episodes, positive SAP among patients with AET < 4%, 4-6%, and > 6% are similar, but MNBI and PSPWi of the patients with AET 4-6% and AET > 6% are lower than AET < 4%. Moreover, the MNBI, PSPWi, and other supportive pH-impedance and manometric evidence suggested by the Lyon consensus between PPI responders and non-responders of patients with AET ≥ 4% are comparable.

After the definition of inconclusive AET in Lyon consensus of GERD, the proper threshold of the AET for pathologic acid reflux in the Chinese population was paid attention to. With our data from 177 patients (69 patients with AET 4-6%), we found reflux symptoms, the proportions of esophagitis, type II/III EGJ, IEM, and PPI response between patients with AET 4-6% and AET > 6% were comparable. Compared with patients with AET < 4%, patients with AET ≥ 4% are with a higher proportion of type II/III EGJ, IEM, and PPI response. Moreover, the MNBI and PSPWi which reflect the esophageal mucosal integrity and chemical clearance ability respectively of the patients with AET ≥ 4% are lower than AET < 4%. Together with 2 Chinese studies from other centers (with 28 and 38 patients with AET between 4-6% respectively)^{5,6} and the 95% CI of the AET of Asian asymptomatic

Table 3. Comparison of 24-Hour pH-Impedance and High-resolution Manometry Parameters Between Proton Pump Inhibitor Responders and Non-responders of Patients With Acid Exposure Time ≥ 4%

Parameters	Responders (n = 87)	Non-responders (n = 35)	P-value	Responder-NERD (n = 63)	Non-responder- NERD (n = 28)	P-value
24-Hour pH-impedance parameters						
AET (%)	8.6 ± 9.9	8.2 ± 12.1	0.849	8.3 ± 10.4	8.5 ± 13.4	0.953
MNBI (Ω)	2121 ± 1045	2212 ± 1075	0.667	2393 ± 1052	2289 ± 1118	0.671
MNBI < 2292	53 (60.9)	20 (57.1)	0.700	32 (50.8)	14 (50.0)	0.944
PSPWi (%)	21.4 ± 13.0	23.0 ± 11.9	0.536	22.2 ± 13.3	22.9 ± 11.9	0.806
PSPWi < 61%	84 (96.6)	35 (100.0)	0.557	60 (95.2)	28 (100)	0.550
Reflux episodes	43.2 ± 34.2	43.9 ± 27.8	0.923	44.1 ± 36.6	36.8 ± 18.5	0.321
Weakly acidic reflux	19.8 ± 22.5	19.4 ± 22.0	0.935	20.6 ± 23.9	14.0 ± 12.1	0.174
Alkaline reflux	0.4 ± 1.7	0.9 ± 2.5	0.248	0.2 ± 1.0	0.4 ± 0.8	0.561
Reflux episodes > 80	9 (10.3)	2 (5.7)	0.509	7 (11.1)	0 (0.0)	0.095
SAP > 95%	36 (41.4)	10 (28.6)	0.187	23 (36.5)	8 (28.6)	0.461
HRM parameters						
EGJ II/III	30 (34.5)	6 (17.1)	0.058	17 (27.0)	3 (10.7)	0.084
Hypotensive EGJ	31 (35.6)	12 (34.3)	0.888	21 (33.3)	10 (35.7)	0.825
IEM	52 (59.8)	22 (62.9)	0.752	37 (58.7)	17 (60.7)	0.859

NERD, non-erosive reflux disease; AET, acid exposure time; MNBI, mean nocturnal baseline impedance; PSPWi, post-reflux swallow-induced peristaltic wave index; SAP, symptom association probability; HRM, high-resolution manometry; EGJ, esophagogastric junction; IEM, ineffective esophageal motility. Data are presented as mean ± SD or n (%).

individuals (2.7-3.9%) from the 2020 Seoul consensus of the management of GERD,⁴ it is reasonable to set 4% as the threshold to define pathological acid reflux for Chinese patients. Indeed, based on the expert's experience and the limited published evidence,^{6,23} the clinical guideline for esophageal ambulatory reflux monitoring in adults released in 2021 by the Gastrointestinal Motility Group, Chinese Society of Gastroenterology made a statement that pathological reflux is considered when AET \geq 4%.²⁴

Impedance parameters were compared between patients with AET \geq 4% and AET < 4%, and we found the total reflux episodes, weakly acid reflux episodes, alkaline reflux episodes, and positive SAP are similar. The MNBI and PSPWi of patients with AET \geq 4% are lower than AET < 4%, and low MNBI and PSPWi are optimal to distinguish patients with GERD (defined as AET \geq 4%) from non-GERD. Furthermore, the MNBI and PSPWi of patients with AET > 6% are lower than patients with AET 4-6%, which means the MNBI and PSPWi correlate with acid burden, and this is consistent with other studies.^{7,10,25} We found the vast majority (97.5%) of patients with AET \geq 4% are with abnormal PSPWi, and this is consistent with another Chinese study,¹³ which means most of the patients with AET \geq 4% have impaired chemical clearance. Regarding the MNBI, in patients with typical reflux symptoms, Rengarajan et al⁷ found only 1.0% of patients with AET > 6% and 8.8% of patients with AET 4-6% are with MNBI \geq 2292 Ω . Ribolsi et al¹⁰ found in true non-erosive reflux disease patients proven by 24-hour pH-MII, 12% of them have MNBI \geq 2292 Ω . Our study demonstrated that in Chinese patients with typical reflux symptoms, 20.8% of patients with AET > 6% and 55.1% of patients with AET 4-6% are with MNBI \geq 2292 Ω . For some patients with AET \geq 4%, their MNBIs are even over 3000 Ω or 4000 Ω . It seems there are some GERD patients with MNBI \geq 2292 Ω , and the proportion of it in China is somewhat higher than Western patients. One possible reason for this difference is the population difference of the MNBI. We noticed that, in Asia, the MNBI of the distal esophagus is higher than in Western countries. The MNBI at 3 cm above LES from Asian healthy volunteers is 3589 (2298, 4554) Ω (represented as median and 25th, 75th percentile values) and from Western healthy volunteers is 2830 (1759, 3826) Ω .²⁶ From the point of the range of the normative values of MNBI, when we define low MNBI, it seems 2292 Ω as the threshold in Asian patients is somewhat reasonable, and the threshold of MNBI for the Western population is supposed to be lower than 2292 Ω . Moreover, we noticed that impedance values from different equipment may be different, the thresholds of 2292 Ω for MNBI and 61.0% for PSPWi are from the Sandhill equipment,⁹

and the pH-impedance catheter we used is from the Given system. More high-quality multi-center studies of asymptomatic individuals and patients with reflux symptoms need to be done to find proper thresholds for different populations and different equipment in the future.

It is believed that low MNBI is associated with acid injury and impaired mucosal integrity.^{9,27} We were eager to know why some GERD patients who have excessive acid exposure are with normal MNBI? We carefully reviewed the motility parameters of the patients with normal MNBI and low MNBI in patients with AET \geq 4%. Fortunately, we found that patients with low MNBI are with more type II or III EGJ. Acid exposure is more severe in patients with low MNBI (Supplementary Table). Interestingly, supine acid reflux episodes recognized through impedance are more predominant in patients with low MNBI, but the upright acid reflux episodes are comparable between patients with low MNBI and normal MNBI. This finding reminds us that when we try to interpret the 24-hour pH-MII results, we need to pay attention to the reflux patterns in different body positions. It is possible for GERD patients whose acid reflux is predominant in the upright position are with normal MNBI. What is the possible reason? As shown in a previous experiment, the recovery of the impedance of healthy humans needs a long time after acid perfusion.²⁸ After perfusion with pH 1.0 for 30 minutes, the recovery of the esophageal impedance was not satisfactory 2 hours after the perfusion (still with a reduction of $47.6 \pm 5.5\%$).²⁸ At the supine position or during bedtime, without the effects of gravity and frequent swallowing of saliva and liquid or food, the clearance of the refluxate may not be easy. The prolonged contact of the esophageal mucosa with the reflux leads to low MNBI.

Many studies have demonstrated that MNBI and PSPWi correlate with PPI response in patients with AET between 4-6% and AET > 6%.^{7,14-16} Unfortunately, in contrast to their results, our study and another Chinese study found that in patients with AET 4-6%, proportions of PPI responders between patients with MNBI \geq 2292 Ω and < 2292 Ω are similar, and they are about 60.0-68.0%.⁶ Moreover, indeed, our data demonstrate in patients with AET \geq 4%, MNBI, PSPWi, AET, and other impedance parameters and manometric parameters between PPI-responders and non-responders are similar. It is not easy for us to predict PPI response based on manometric and pH-impedance parameters.

We have a few limitations. First, this is a retrospective study, and subjects were searched from the motility laboratory database. There may be some selection bias because not all suspected GERD patients entered this study. Second, a small portion of participants

accepted 24-hour pH-MII without previous use of PPI, their PPI responses were collected from the medical records or phone calls. However, when we communicated with the patients, it was easy for them to recall the symptom improvement because they were impressed by the HREM and 24-hour monitoring procedures, and they paid attention to the treatment effect after the impressive procedures. PPI use compliance is not easy for us to check for these patients, and prospective studies will be performed in the future.

In conclusion, it is reasonable to set 4% as the threshold to define physiological and pathological acid exposure in the Chinese population. MNBI and PSPWi are helpful to distinguish GERD patients. The vast majority of GERD patients are with PSPWi < 61%, and about 60% of GERD (defined as AET \geq 4%) patients are with MNBI < 2292 Ω . If the acid reflux is not predominant in the supine position, the MNBI could be normal. MNBI, PSPWi, and AET may not correlate with PPI response in GERD patients with typical reflux symptoms. Future studies need to be performed to find proper thresholds to define abnormal impedance-pH metrics for different populations and different devices.

Supplementary Material

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at <http://www.jnmjournal.org/>, and at <https://doi.org/10.5056/jnm21156>.

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