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Mean nocturnal baseline impedance, a novel metric of multichannel intraluminal impedance-pH monitoring in diagnosing gastroesophageal reflux disease

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***Abstract*:** Gastroesophageal reflux disease (GERD) is a common disease with increasing prevalence worldwide. However, the diagnosis of GERD is challenging because there are no definite gold standard criteria. Recently, a novel impedance parameter, namely mean nocturnal baseline impedance (MNBI), has been proposed, which reflects the burden of longitudinal reflux and the integrity of esophageal mucosa. MNBI has shown an immense promise for increasing the diagnostic rate of multichannel intraluminal impedance-pH (MII-pH) monitoring and predicting the response to proton pump inhibitor (PPI) or anti-reflux intervention in patients with reflux symptoms. The present paper reviews the association between baseline impedance and esophageal mucosal integrity, the acquisition of MNBI in 24-h MII-pH monitoring, the clinical utilization of MNBI in improving the diagnosis rate of GERD in patients with typical reflux symptoms, predicting the response to PPI or anti-reflux treatment in these patients, the utilization of MNBI in diagnosing patients with atypical symptoms or extra-esophageal symptoms, and the correlation between reflux burden and MNBI. MNBI should be routinely assessed using MII-pH monitoring.

Keywords: gastroesophageal reflux disease, mean nocturnal baseline impedance, multichannel intraluminal impedance-pH monitoring

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Introduction

The estimated worldwide prevalence of gastroesophageal reflux disease (GERD) is 8–33%.[1] The diagnosis of GERD is clinically challenging due to the multifactorial pathophysiology mechanisms of GERD, including esophageal mucosal integrity, competent esophagogastric junction, esophageal peristalsis, etc. Upper endoscopy and multichannel intraluminal impedance-pH (MII-pH) monitoring are usually performed to provide objective evidence for pathological reflux. However, 70% of the patients with heartburn have no macroscopic evidence of esophageal mucosal injuries.[2] In addition, the diagnostic sensitivity of conventional metrics [i.e. acid exposure time (AET), symptom association probability (SAP), and symptom index (SI)] in MII-pH monitoring is considered to be suboptimal.[3–5] AET is the most useful conventional parameter to distinguish pathological reflux from physiological reflux, but it was normal in 19% of the patients with erosive esophagitis (EE)[3] and nearly 50% of the patients with non-erosive reflux disease (NERD),[3,4] possibly due to the day-to-day variability of AET.[6] The diagnostic sensitivity of positive SI (SI $>50\%$), positive SAP (SAP $>95\%$), and concordant SAP/SI positivity (SAP $>95\%$ and SI $>50\%$) for the diagnosis of GERD was 51.06%, 46.81%, and 36.17%, respectively.[5]

Recently, the utilization of baseline impedance (BI), which is a surrogate marker of mucosal integrity and is resistant to circadian variations,[7] has been proposed for the diagnosis of GERD

clinically. This application is mainly based on the following aspects. The barrier protection of the esophageal mucosa can be impaired by reflux, which may cause dilated intercellular spaces (DIS). In 2011, a seminal study by Farré *et al.*[8] found that esophageal perfusion with the acidic solution in rabbits induced a significant increase in DIS and a decrease in impedance. Moreover, biopsy specimens from patients with EE or NERD had significant DIS compared to patients with functional heartburn (FH)[9–12] and healthy controls,[9,10,12–14] indicating DIS was a significant histological abnormality of GERD patients and a known marker of esophageal mucosal integrity.[7,11,13] However, the application of DIS is limited in clinical practice because of the complicated protocol and the need for a dedicated esophageal pathologist. Therefore, BI as a surrogate marker of mucosal integrity which is more applicable has been proposed for GERD diagnosis. DIS can increase the permeability of esophageal epithelium and the flow of ion-rich fluid around the cells, resulting in a decrease in the BI of GERD.[7,8,11,13,15] In addition, BI is negatively correlated with DIS and AET in the distal esophagus (Table 1).[11,13,15] In addition, lower BI can be improved by an effective anti-reflux surgery in patients with proton pump inhibitor (PPI) refractory typical GERD symptoms.[16]

Esophageal BI can be obtained by several ways. It can be determined by MII-pH monitoring during the night avoiding swallows as mean nocturnal BI (MNBI). Also, BI can be acquired from an impedance probe with a high-resolution impedance manometry (HRIM) as BI-HRIM or from a catheter-based probe during sedated endoscopy as mucosal impedance. The MII-pH monitoring technology is widely used clinically. In addition, MNBI as a novel impedance metric can be acquired from available information in an esophageal MII-pH study. Moreover, MNBI can reflect longitudinal reflux burden objectively and has a high inter-observer concordance rate.[4] Therefore, this article reviewed the utility of MNBI in GERD.

The acquisition of MNBI in 24-h MII-pH monitoring

There are six impedance channels (Z1–Z6) in MII-pH monitoring, located at 17, 15, 9, 7, 5, and 3 cm above the lower esophageal sphincter (LES),

Table 1. The association between BI and DIS.

Author	Subject groups	DIS (μm)	BI (Ω)	AET (%)	Correlation	
					DIS and BI	BI and AET
Zhong *et al.*[13]	EE ($n=79$)	1.29 (1.10–1.46)	1752 ± 1018	18.9 (10.1–27.9)	$r=-0.637$ $p<0.001$	$r=-0.41$ $p<0.001$
	NERD ($n=150$)	1.10 (0.95–1.21)	2640 ± 1143	6.4 (4.5–12.1)		
	Controls ($n=34$)	1.01 (0.94–1.17)	3360 ± 1258	1.4 (0.6–3.0)		
Kandulski *et al.*[11]	EE ($n=16$)	–	994.0 ± 182.2	6.1 ± 1.8	$r=-0.28$ $p=0.06$	$r=-0.45$ $p=0.008$
	NERD ($n=19$)	–	1558 ± 362.3	5.1 ± 1.0		
	FH ($n=17$)	–	2884 ± 364.8	0.8 ± 0.2		
Xie *et al.*[15]	EE ($n=35$)	0.94 ± 0.17	1571.09 ± 567.54	–	$r=-0.230$ $p<0.05$	$r=-0.527$ $p<0.01$
	NERD ($n=29$)	0.89 ± 0.20	1581.07 ± 494.61	–		
	RH ($n=28$)	0.85 ± 0.19	2156.01 ± 495.55	–		
	Controls ($n=10$)	0.66 ± 0.11	2364.67 ± 500.70	–		

AET, acid exposure time; BI, baseline impedance; DIS, dilated intercellular spaces; EE, erosive esophagitis; FH, functional heartburn; NERD, non-erosive reflux disease; RH, reflux hypersensitivity.

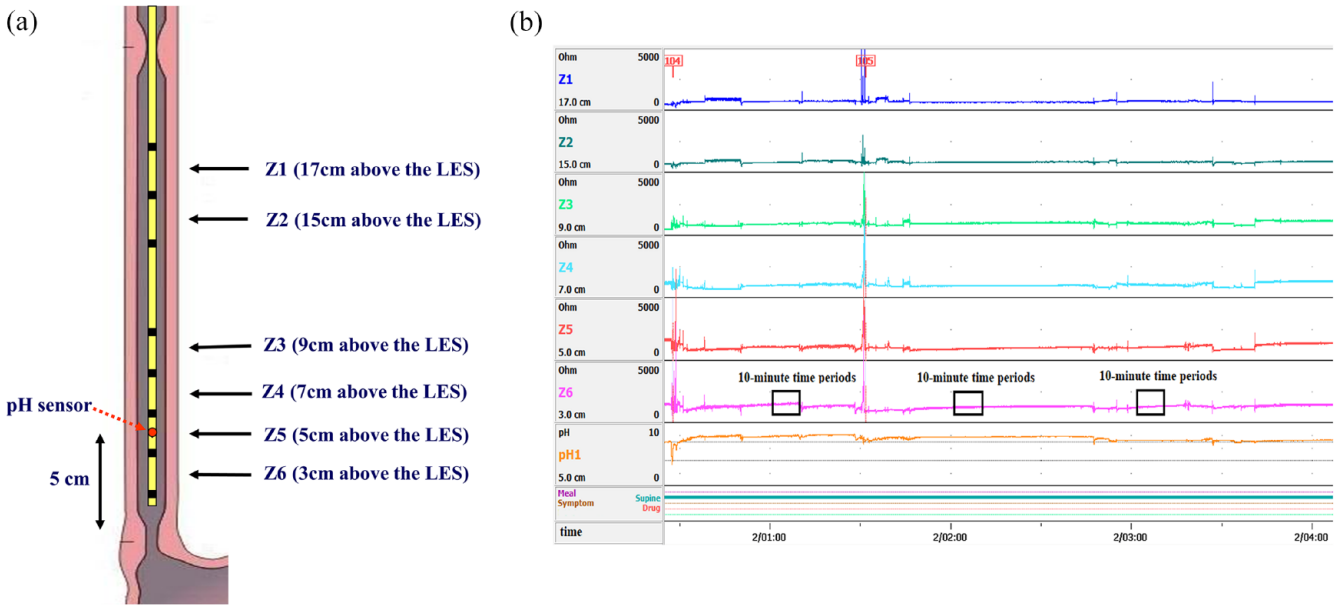

Figure 1. (a) Illustration of a 24-h MII-pH catheter with six impedance channels (Z1–Z6) (located at 17, 15, 9, 7, 5, and 3 cm above the LES, respectively) and an esophageal pH sensor. (b) The acquisition of MNBI. Three stable 10-min time periods (around 1 a.m., 2 a.m., and 3 a.m.) avoiding swallows, reflux episodes, artifacts, or pH drops are selected. The BI values of the three time periods are averaged to obtain the MNBI.
LES, lower esophageal sphincter; MII-pH, multichannel intraluminal impedance-pH; MNBI, mean nocturnal baseline impedance.

respectively [Figure 1(a)]. The standardized measurement of MNBI in MII-pH monitoring was obtained by calculating the BI of impedance channel at 3 cm above the LES, which was first proposed by Martinucci *et al.*[17] Three stable 10-min time periods (around 1 a.m., 2 a.m., and 3 a.m.) avoiding swallows, reflux episodes, artifacts, or pH drops were selected when the patient was in a supine position. Subsequently, the average BI for each time period was computed with the aid of the software [Figure 1(b)]. The BI values of the three time periods were averaged to get the MNBI, which can accurately reflect the BI of a 6-h nocturnal bedtime period.[17] Subsequently, this formula was widely used in most studies. However, there are subtle variations in the selected impedance channel in some other studies, such as the impedance channel at 5 cm above the LES[15,18,19] or the distal four channels (mean MNBI value of Z3–Z6).[20]

The utilization of MNBI in patients with typical reflux symptoms

Increasing the diagnostic rate of GERD

Previous studies have demonstrated that MNBI can improve the diagnostic rate of GERD in patients with typical reflux symptoms.[4,5,15,16,18,19,21–28] Lower MNBI values have been found in EE, NERD, and reflux hypersensitivity (RH) compared with FH and healthy controls.[4,15,16,18,19,21–23] Also, MNBI was significantly lower in patients with refractory reflux esophagitis than in those with healed reflux esophagitis and NERD, indicating that low MNBI could reflect the severity of esophageal mucosal damage.[16] In addition, it has been proved to be useful in distinguishing GERD from healthy controls,[4,15,21] and distinguishing reflux-related patients (GERD[16,18,19,22] and RH[22,23]) from reflux-unrelated patients (FH) with a high diagnostic accuracy (Table 2). Moreover, MNBI may be particularly useful in patients with inconclusive GERD.[27,28]

Separating GERD from healthy controls. As far as we know, three studies evaluated the value of MNBI in distinguishing GERD from healthy controls.[4,15,21] Frazzoni *et al.*[4] prospectively conducted a multicenter study on 289 GERD patients and 50 healthy controls in Italy who underwent 24-h MII-pH monitoring, showing that 2292 Ohm (Ω) could be used as the cutoff impedance values to discriminate GERD from healthy individuals. Subsequently, the fixed MNBI threshold

Table 2. The utilization of MNBI in increasing the diagnostic rate of GERD and predicting the response to PPI or anti-reflux treatment in patients with typical reflux symptoms.

Author	Off PPI or on PPI MII-pH	Subject groups	Group classification criteria	Assessment of the MNBI	MNBI (Ω)	Application of MNBI
Distinguishing GERD from Healthy controls						
Frazzoni *et al.*[4]	Off PPI for at least 2 weeks	EE ($n=68$)	With esophagitis	3 cm above the LES	1129 ± 654	With an AUC 0.876 (95% CI 0.833–0.918) at a cutoff value of 2292 Ω
		NERD ($n=221$)	Normal endoscopy with positive pH or with negative pH		1789 ± 812	
		HC ($n=50$)			2936 ± 772	
Xie *et al.*[15]	Not mentioned	EE ($n=35$)	With esophagitis	5 cm above the LES	1571.09 ± 567.54	With an AUC 0.794 at a cutoff value of 1764 Ω
		NERD ($n=29$)	Normal endoscopy, but AET $\geqslant$ 4%		1581.07 ± 494.61	
		RH ($n=28$)	Normal endoscopy, AET $<$ 4% and SAP $\geqslant$ 95%		2156.1 ± 495.55	
		HC ($n=10$)			2364.67 ± 500.70	
Frazzoni *et al.*[21]	Off PPI for 2 weeks	PPI dependent	Troublesome heartburn (score 2–3)	3 cm above the LES	1565 ± 837	With an AUC 0.89 (95% CI 0.86–0.92) at a cutoff value of 2000 Ω
		Heartburn ($n=488$)	Suppressed (score 0–1) by 4-week standard-dosage PPI therapy, early recurring after PPI wash out and again early suppressed by 4-week standard-dosage PPI			
		HC ($n=70$)			2990 ± 835	
Separating NERD from FH						
Tenca *et al.*[18]	Off-PPI for at least 10–14 days	NERD ($n=25$)	Normal endoscopy findings and AET $>$ 4.2%	5 cm above the LES	971 ± 180	With an AUC 0.960 at a cutoff value of 2934 Ω, with a sensitivity of 88% and a specificity of 80%
		FH ($n=25$)	AET $<$ 4.2%, normal total number of reflux events, and negative SAP/SI[a]		3889 ± 728	
Yoshimine *et al.*[19]	Not mentioned	NERD ($n=59$)	AET $>$ 4.2% or positive SI/SAP[b]	5 cm above the LES	2229.9 ± 1042.9	With an AUC 0.73 (95% CI 0.63–0.84) at a cutoff value of 2874.1 Ω, with a sensitivity of 68.5% and a specificity of 72.8%
		FH ($n=32$)	AET $<$ 4.2% and negative SI/SAP[a]		3061.2 ± 762.1	

(Continued)

Table 2. (Continued)

Author	Off PPI or on PPI MII-pH	Subject groups	Group classification criteria	Assessment of the MNBI	MNBI (Ω)	Application of MNBI
Frazzoni *et al.*[16]	On PPI therapy	RRE ($n=39$)	Persistence of mucosal breaks	3 cm above the LES	1145 (662–1879)	With an AUC 0.677 (95% CI 0.605–0.748), with a sensitivity of 43% and a specificity of 93%
		HRE ($n=41$)	Regressions of mucosal breaks		1741 (1273–2951)	
		NERD ($n=68$)	Negative endoscopy findings, but AET > 3.2%, and/or number of reflux events < 48, and/or positive SAP/SI[b]		2374 (1755–2835)	
		FH ($n=41$)	Negative endoscopy findings, AET < 3.2%, number of reflux events < 48, and negative SAP/SI[a]		3488 (2965–4069)	
Frazzoni *et al.*[22]	Off PPI for 2 weeks	NERD ($n=125$)	PPI-responsive heartburn, endoscopy negative, abnormal AET	3 cm above the LES	1378 ± 699	With a sensitivity of 86% and a specificity of 94%
		FH ($n=70$)	Endoscopy-negative heartburn unaffected by PPI therapy, normal AET, and negative SAP/SI[a]		3443 ± 873	
Distinguishing RH from FH						
Frazzoni *et al.*[22]	Off PPI for 2 weeks	RH ($n=108$)	Negative upper endoscopy, normal AET, positive SAP/SI[b]	3 cm above the LES	2274 ± 774	With an AUC 0.864 (95% CI 0.809–0.919), with a sensitivity of 56% and a specificity of 94%
		FH ($n=70$)	Endoscopy-negative heartburn unaffected by PPI therapy, normal AET, and negative SAP/SI[a]		3443 ± 873	
Gao *et al.*[23]	Off PPI for a week	FH ($n=147$)	Normal endoscopy, normal AET, negative SAP/SI[a]	3 cm above the LES	2972.0 ± 775.6	With an AUC 0.643 (95% CI 0.570–0.716)
		RH ($n=91$)	Normal endoscopy and AET, but positive SAP/SI[b]		2485.3 ± 939.2	
Identification of GERD						
Jiang *et al.*[5]	Off anti-reflux therapy for at least 7 days	AET < 4% ($n=72$)	The Lyon Consensus	5 cm above the LES	3388.5 ± 1639.5	With an AUC 0.839 at a cutoff value of 1838Ω, with a sensitivity of 76.6% and a specificity of 81.0%

(Continued)

Table 2. (Continued)

Author	Off PPI or on PPI MII-pH	Subject groups	Group classification criteria	Assessment of the MNBI	MNBI (Ω)	Application of MNBI
		AET 4–6% ($n=28$)			1911 ± 1464	
		AET > 6% ($n=47$)			1131 ± 1168	
Ravi *et al.*[24]	Not mentioned	GERD ($n=29$)	pH < 4 for ⩾5% of both the supine and total study time	3 cm above the LES	1331.3 ± 232.9	With an AUC 0.891 at a cutoff value of 2268.1 Ω, with a sensitivity of 86.2% and a specificity of 80.8%
		Controls ($n=26$)	pH ⩽ 3% of the MII-pH study off PPI		3397.4 ± 246	
Hoshikawa *et al.*[25]	Off PPI for at least 7 days	EE ($n=20$)	With esophagitis	3 cm above the LES	854 (509–1318)	Diagnosis of GERD (EE + NERD) with an AUC 0.872 at a cutoff value of 1785 Ω, with a sensitivity of 82.5% and a specificity of 89.7%
		NERD ($n=20$)	Negative endoscopy and AET > 6%		1370 (812–1773)	
		RH ($n=20$)	Negative endoscopy, AET < 4%, and positive SAP/SI[b]		2631 (1970–3680)	
		FH ($n=20$)	Negative endoscopy, AET < 4%, and negative SAP/SI[a]		3200 (2270–4113)	
Wong *et al.*[26]	Off PPI for at least 7 days	GERD ($n=20$)	EE or AET ⩾ 4%	3 cm above the LES	1385.2 ± 183.7	With an AUC 0.865 at a cutoff value of 2128 Ω, with a sensitivity of 77.8% and a specificity of 84.2%
		Non-GERD ($n=28$)	No fulfillment above criteria		2608.3 ± 123.1	
Predicting the response to PPI or anti-reflux treatment						
Frazzoni *et al.*[29]	After 2-week PPI withdrawal	PPI responsive ($n=317$)	Troublesome heartburn (score 2–3) suppressed (score 0–1) by 4-week PPI therapy	3 cm above the LES	1681 ± 897	Linking PPI-responsive heartburn to reflux better than AET (with AUC 0.742 *versus* 0.687, $p<0.001$)
		PPI refractory ($n=108$)	Troublesome heartburn (score 2–3) unaffected by at least 8-week double-dosage PPI therapy		2812 ± 1199	
Ribolsi *et al.*[28]	Off PPI for at least 7 days	Responders ($n=145$)	Symptom improvement ⩾50%	3 cm above the LES	1545.6 ± 826 Ω	Pathological MNBI (<2292 Ω) was significantly associated with PPI response
		Non-responders ($n=88$)	Symptom improvement <50%		2385.9 ± 825.5	
Patel *et al.*[20]	Off PPI for 5–7 days	Responder ($n=57$)	⩾50% improvement in GSS	The average of distal 4 channels	1921.8 ± 127.1	Predicting GSS improvement to anti-reflux therapy

(Continued)

Table 2. (Continued)

Author	Off PPI or on PPI MII-pH	Subject groups	Group classification criteria	Assessment of the MNBI	MNBI (Ω)	Application of MNBI
		Non-responder ($n=31$)	Without ⩾50% GSS improvement		2324.1 ± 197.1	
Xie *et al.*[15]	Not mentioned	PPI effective ($n=60$)	Symptom-free or with only one mild episode during the final week of the therapy otherwise the therapy was considered a failure	5 cm above the LES	1621.26 ± 561.17	The BI >1764 Ω was the only independent predictor for the PPI failure
		PPI failure ($n=13$)			2117.48 ± 428.68	
Ribolsi *et al.*[30]	Off PPI for at least 7 days	Responders ($n=99$)	Symptom improvement ⩾50%	3 cm above the LES	1607 ± 235	Normal MNBI (>2292 Ω) was associated with an unfavorable response to PPIs
		Non-responders ($n=105$)	Symptom improvement <50%		2108 ± 412	
de Bortoli *et al.*[31]	Off PPI for 14 days	FH/PPI responders ($n=40$)	⩾50% Symptom improvement of FH patients	3 cm above the LES	1949.6 ± 548.8	Identification of patients who respond to PPIs but would be classified as having FH
		FH/PPI-non responders ($n=40$)	<50% Symptom improvement of FH patients		3812.8 ± 810.2	
		RH ($n=40$)	Normal endoscopy, AET, number of reflux episodes, but positive SAP/SI[b]		1839.7 ± 467.6	

[a]SAP < 95% and SI < 50%.
[b]SAP ⩾ 95% and/or SI ⩾ 50%.
AET, acid exposure time; AUC, area under the curve; CI, confidence interval; EE, erosive esophagitis; FH, functional heartburn; GERD, gastroesophageal reflux disease; GSS, global symptom severity; HC, healthy controls; HRE, healed reflux esophagitis; LES, lower esophageal sphincter; MII-pH, multichannel intraluminal impedance-pH; MNBI, mean nocturnal baseline impedance; NERD, non-erosive reflux disease; PPI, proton pump inhibitor; RH, reflux hypersensitivity; RRE, refractory reflux esophagitis; SAP, symptom association probability; SI, symptom index.

(2292 Ω) was used by many studies[16,20,27–30] and was mentioned in the Lyon Consensus.[32] Recently, a large multicenter cohort from Italy enrolled 488 patients with PPI-dependent heartburn and 70 healthy controls found that MNBI showed high efficiency in identifying patients with PPI-dependent heartburn with an area under the curve (AUC) of 0.89 at a cutoff value of 2000 Ω.[21] However, the normative MNBI thresholds may vary between ethnicities and regions. Another study from China suggested that 1764 Ω can be used as the MNBI threshold to distinguish patients from healthy individuals, which involved 92 patients with typical reflux symptoms and 10 healthy controls.[15] Given this, the cutoff value of pathological MNBI may be lower in Asia than in Europe. Future studies involving normative MNBI values of different ethnicities and regions are warranted.

Distinguishing NERD from FH. It is crucial to distinguish GERD from non-GERD for prescribing different treatments. The diagnosis of NERD may be missed if only based on the conventional pH-impedance metrics. MNBI analysis could complement conventional pH-impedance metrics in differentiating GERD from FH in patients with typical reflux symptoms, which was crucial for prescribing different treatments. Frazzoni *et al.*[4] showed that MNBI could improve the diagnostic rate of NERD classified by Rome III criteria. Abnormal MNBI can identify NERD patients who may not be confirmed by conventional metrics in MII-pH monitoring (AET and SAP/SI). 83% (183/216) of NERD patients can be confirmed using AET and SAP/SI.[4] When adding cases whose only abnormality was an abnormal MNBI, the proportion of diagnosed NERD was significantly increased.[4] Sun *et al.*[33] found that 16.67% (13/78) of FH diagnosed by conventional parameters in 24-h MII-pH monitoring may be GERD patients according to abnormal MNBI. If the MII-pH monitoring period prolongs to 48 h, 72 h, or 96 h, the 16.67% (13/78) patients who were classified as FH by conventional metrics in 24-h MII-pH monitoring can be re-classified as NERD.[33] Moreover, previous studies have demonstrated that MNBI can be useful for distinguishing NERD from FH with high AUC, high sensitivity, and specificity off PPI or on PPI therapy (Table 2).[16,18,19,22]

Separating RH from FH. It is important to differentiate RH from FH in the clinic because RH may also benefit from anti-reflux therapy.[34] Patients with RH and FH have no objective evidence of reflux (normal endoscopy and normal AET), but there is a positive reflux-symptom association (positive SAP or SI) in patients with RH.[35] However, a negative SAP/SI may not rule out RH. SI and SAP rely excessively on the accuracy of patients' records and patients may not perceive symptoms during 24-h MII-pH monitoring. In addition, SAP and SI can be influenced by day-to-day variability, degree of reflux, and length of monitoring in patients with reflux symptoms.[36] Moreover, the positive reflux-symptom association may be influenced by low reflux events.[36]

Even in the case of normal reflux events, MNBI as an objective metric can differentiate RH from FH.[22,23,31] Recently, studies have found that MNBI was significantly lower in RH than in FH and it can separate RH from FH independently of SAP and SI (Table 2).[22,23] In addition, the MNBI of PPI responders was significantly lower than that of PPI non-responders among patients with FH.[31] Also, the MNBI value of PPI responders in patients with FH was similar to that of patients with RH, indicating that PPI responders in FH patients may be classified as RH based on MNBI.[31] RH is characterized by DIS, which can explain the increased perception of reflux events and the positive response to anti-reflux treatment.[22] Therefore, the MNBI should be evaluated to help physicians to distinguish between RH and FH if reflux-symptom association afford uncertain results (i.e. poor accuracy in symptom recording, or discordant SAP and SI).

Acting as supportive evidence for inconclusive GERD. The Lyon Consensus has proposed stricter criteria for GERD diagnosis. MNBI has been proposed as an adjunctive evidence for patients with inconclusive GERD (AET 4–6%, Los Angeles A or B esophagitis, or reflux events 40–80) by the Lyon Consensus.[32] Several studies have demonstrated that MNBI may be particularly useful in patients with inconclusive results of traditional variables in MII-pH monitoring.[21,27,28]

A study involving two tertiary medical centers by Rengarajan *et al.*[27] demonstrated that inconclusive AET (4–6%) can be divided into two categories based on whether MNBI is abnormal. 91.8% (67/73) of patients had abnormal MNBI (<2292 Ω) among patients with inconclusive AET. Among patients with abnormal MNBI,

73.1% (49/67) of patients responded to anti-reflux therapy, which was comparable to that seen with pathological AET [75.7% (84/111)].[27] However, among patients with normal MNBI (>2292 Ω), 33.3% (2/6) of patients responded to anti-reflux therapy, which was similar to patients with physiological AET (27/70, 38.6%).[27] Recently, Frazzoni *et al.*[21] conducted a large multicenter cohort of 488 patients with PPI-dependent heartburn and with 70 healthy controls, which found that the diagnosis of GERD was confirmed by MNBI in 75% of patients with inconclusive AET (4–6%), showing the high clinical value of MNBI for the diagnosis of GERD in such cases. Ribolsi *et al.*[28] performed a multicenter study that enrolled 233 patients with typical reflux symptoms in Italy, which showed that pathological MNBI (<2292 Ω) was significantly associated with PPI response in inconclusive GERD patients. In addition, MNBI can distinguish between PPI responders and PPI non-responders among inconclusive GERD patients with an AUC 0.89 at a cutoff value of 1916 Ω, with a sensitivity of 80% and a specificity of 91.4%.[28] All these studies demonstrated that abnormal MNBI can sway clinical impression toward conclusive GERD in patients with inconclusive GERD.[21,27,28] Evaluation of MNBI may be especially crucial for inconclusive GERD patients if they are candidates for anti-reflux surgical or endoscopic interventions.

The use of MNBI in predicting the response to PPI or anti-reflux therapy

The currently available literature has demonstrated that MNBI was significantly lower in responders than in non-responders to PPI or anti-reflux therapy, and MNBI can predict the response to PPI or anti-reflux therapy in patients with typical reflux symptoms (Table 2).[15,17,20,27–31] Some studies pointed out that abnormal MNBI (<2292 Ω) was independently associated with PPI response or anti-reflux therapy in patients with typical reflux symptoms.[20,27,28] Likewise, some other studies found that MNBI > 2292 Ω[30] or MNBI > 1764 Ω[15] was associated with PPI failure in patients with typical reflux symptoms. Frazzoni *et al.*[29] found that MNBI can predict the symptomatic response to PPI treatment better than AET (AUC 0.742 *versus* AUC 0.687, $p = 0.003$). In addition, among FH patients, the MNBI was significantly lower in PPI responders than in PPI non-responders, and MNBI can also predict the response of these patients to PPI.[17,31] Furthermore, MNBI may be of particular value in identifying patients who were responsive to PPI or anti-reflux therapy in patients with inconclusive GERD, which can help identify GERD patients among these patients.[27,28]

The use of MNBI in diagnosing patients with atypical symptoms or extra-esophageal symptoms

Few data are available concerning MNBI in patients with atypical symptoms or extra-esophageal symptoms (EES).[37–42] Zhong *et al.*[37] demonstrated that in MII-pH monitoring, the BI (Z2–Z6) of GERD patients with chest pain syndrome and EES was significantly lower than that of healthy controls. Ribolsi *et al.*[38] studied 239 EES patients in Italy. They showed that distal MNBI (3 cm above the LES) was significantly lower in patients with PPI response than in those with PPI non-response. And abnormal MNBI (<2292 Ω) was associated with PPI response in patients with EES.[38] In addition, Sakin *et al.*[39] displayed that proximal-to-distal BI ratio [(mean Z1 + Z2)/(mean Z5 + Z6)] can be useful in diagnosing patients with laryngopharyngeal reflux (LPR) symptoms. Moreover, Chen *et al.*[40] found that proximal MNBI (15 or 17 cm above the LES) can not only identify patients with LPR, but also predict outcomes to anti-reflux therapy. However, some other studies noted that MNBI was not sufficient to evaluate patients with EES.[41,42] Doo *et al.*[41] showed that there was no significant difference in the MNBI values of distal and proximal esophageal (Z6 and Z3, respectively) between patients with LPR and healthy controls. In addition, Zikos *et al.*[42] found that there was no correlation between distal/proximal MNBI and EES. Whether MNBI can improve the diagnostic rate of GERD patients or predict the response to anti-reflux therapy in patients with EES or atypical symptoms is an open question to be explored in future studies.

Correlation between reflux burden and MNBI

Previous studies showed that MNBI was significantly lower in patients with AET > 6% than in patients with AET 4–6% or in patients with AET < 4%.[21,43] The proportion of abnormal MNBI was significantly higher in patients with AET > 6% or AET 4–6% than in patients with

AET > 4%.[27] Ribolsi *et al.*[44] prospectively performed a multicenter study that enrolled 230 patients with dominant typical esophageal symptoms, which demonstrated that AET was negatively correlated with MNBI values. In addition, AET > 4% was significantly associated with abnormal MNBI values.[44] The correlation between AET and MNBI may be that the increased reflux burden results in the impaired integrity of esophageal mucosa, as shown by decreased MNBI values.

Concerns and future directions

The calculation of MNBI is easy to obtain from MII-pH monitoring. In addition, just like glycated hemoglobin A1c *versus* blood glucose measurement in diagnosing diabetes mellitus, we thought that MNBI might be more stable and reflect relatively longer periods of reflux when comparing with conventional parameters, such as AET and SAP/SI, etc. However, there are concerns about the reliability of the MNBI measurement. If the impedance sensors are not in close contact with the esophageal mucosa due to the presence of reflux episodes and swallows,[19] or calculation of MNBI is influenced by artifacts and pH drop, MNBI may be compromised. Given this, when analyzing the MNBI value, we should select three 10-min time periods with caution to avoid reflux episodes, swallows, artifacts, and pH drop.[17] Moreover, low MNBI can be observed not only in GERD patients, but also in the presence of eosinophilic esophagitis[45] and severe esophageal motility disorders, such as absent peristalsis and achalasia,[46] which should also be considered.

Notably, the spectrum and diagnostic criteria of GERD vary across different studies. RH is included in the GERD phenotype in the Rome III criteria.[47] However, it has been excluded from the GERD phenotype and included in the spectrum of functional disorders in Rome IV criteria.[35] In addition, the diagnostic criteria for GERD vary among studies. The Lyon Consensus proposed stricter criteria for GERD diagnosis, including advanced grades of EE (Los Angeles C or D esophagitis), AET > 6%, long-segment Barrett's esophagus, or peptic esophageal stricture.[32] However, GERD was defined by lower AET thresholds (AET > 4%[15,18,19,26] or AET > 3.2%[16]) or defined by macroscopic evidence of esophageal mucosal injuries regardless of grades in some previous studies.[4,15,26] Although previous studies had adopted different diagnostic criteria of GERD, they have consistently shown that MNBI can reflect esophageal mucosal integrity and can display the clinical value of MNBI for the diagnosis of GERD in patients with reflux symptoms.

In addition, because MNBI cannot be obtained from software analysis automatically, it takes extra minutes to calculate MNBI during the manual analysis of tracings. The previous study has claimed that artificial intelligence (AI) can accurately and instantaneously extract meaningful metrics from pH-impedance monitoring by automating the recognition, censoring, and removal of esophageal events.[48] We believe that MNBI may be automatically extracted by AI in the future.

Conclusion

As an objective and reproducible parameter for MII-pH monitoring, MNBI can not only improve the diagnostic rate of GERD in patients with reflux symptoms, but also predict the response to PPI or anti-reflux therapy in these patients. Therefore, MNBI should be routinely assessed using MII-pH monitoring.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Yanhong Wu: Investigation; Methodology; Writing – original draft.

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Chuan Zhang: Conceptualization; Investigation; Supervision; Validation; Writing – review & editing.

Yutao Zhan: Conceptualization; Investigation; Supervision; Validation; Writing – review & editing.

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Competing Interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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References

1. El-Serag HB, Sweet S, Winchester CC, *et al*. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014; 63: 871–880.
2. Matsumura T, Ishigami H, Fujie M, *et al*. Endoscopic-guided measurement of mucosal admittance can discriminate gastroesophageal reflux disease from functional heartburn. *Clin Transl Gastroenterol* 2017; 8: e94.
3. Savarino E, Tutuian R, Zentilin P, *et al*. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. *Am J Gastroenterol* 2010; 105: 1053–1061.
4. Frazzoni M, Savarino E, de Bortoli N, *et al*. Analyses of the post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters increase the diagnostic yield of impedance-pH monitoring of patients with reflux disease. *Clin Gastroenterol Hepatol* 2016; 14: 40–46.
5. Jiang Y, Jiang L, Ye B, *et al*. Value of adjunctive evidence from MII-pH monitoring and high-resolution manometry in inconclusive GERD patients with AET 4-6. *Therap Adv Gastroenterol* 2021; 14: 17562848211013484.
6. Penagini R, Sweis R, Mauro A, *et al*. Inconsistency in the diagnosis of functional heartburn: usefulness of prolonged wireless pH monitoring in patients with proton pump inhibitor refractory gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2015; 21: 265–272.
7. Kessing BF, Bredenoord AJ, Weijenborg PW, *et al*. Esophageal acid exposure decreases intraluminal baseline impedance levels. *Am J Gastroenterol* 2011; 106: 2093–2097.
8. Farré R, Blondeau K, Clement D, *et al*. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. *Gut* 2011; 60: 885–892.
9. Kandulski A, Jechorek D, Caro C, *et al*. Histomorphological differentiation of non-erosive reflux disease and functional heartburn in patients with PPI-refractory heartburn. *Aliment Pharmacol Ther* 2013; 38: 643–651.
10. Vela MF, Craft BM, Sharma N, *et al*. Refractory heartburn: comparison of intercellular space diameter in documented GERD vs. functional heartburn. *Am J Gastroenterol* 2011; 106: 844–850.
11. Kandulski A, Weigt J, Caro C, *et al*. Esophageal intraluminal baseline impedance differentiates gastroesophageal reflux disease from functional heartburn. *Clin Gastroenterol Hepatol* 2015; 13: 1075–1081.
12. Cui R, Zhang H, Zhou L, *et al*. Diagnostic value of dilated intercellular space and histopathologic scores in gastroesophageal reflux disease. *Dis Esophagus* 2015; 28: 530–537.
13. Zhong C, Duan L, Wang K, *et al*. Esophageal intraluminal baseline impedance is associated with severity of acid reflux and epithelial structural abnormalities in patients with gastroesophageal reflux disease. *J Gastroenterol* 2013; 48: 601–610.
14. Cui R, Zhou L, Lin S, *et al*. The feasibility of light microscopic measurements of intercellular spaces in squamous epithelium in the lower-esophagus of GERD patients. *Dis Esophagus* 2011; 24: 1–5.
15. Xie C, Sifrim D, Li Y, *et al*. Esophageal baseline impedance reflects mucosal integrity and predicts symptomatic outcome with proton pump inhibitor treatment. *J Neurogastroenterol Motil* 2018; 24: 43–50.
16. Frazzoni M, de Bortoli N, Frazzoni L, *et al*. The added diagnostic value of postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance in refractory reflux disease studied with on-therapy impedance-pH monitoring. *Neurogastroenterol Motil* 2017; 29: e12947.

17. Martinucci I, de Bortoli N, Savarino E, *et al*. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. *Neurogastroenterol Motil* 2014; 26: 546–555.

18. Tenca A, de Bortoli N, Mauro A, *et al*. Esophageal chemical clearance and baseline impedance values in patients with chronic autoimmune atrophic gastritis and gastro-esophageal reflux disease. *Dig Liver Dis* 2017; 49: 978–983.

19. Yoshimine T, Funaki Y, Kawamura Y, *et al*. Convenient method of measuring baseline impedance for distinguishing patients with functional heartburn from those with proton pump inhibitor-resistant endoscopic negative reflux disease. *Digestion* 2019; 99: 157–165.

20. Patel A, Wang D, Sainani N, *et al*. Distal mean nocturnal baseline impedance on pH-impedance monitoring predicts reflux burden and symptomatic outcome in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2016; 44: 890–898.

21. Frazzoni L, Frazzoni M, De Bortoli N, *et al*. Application of Lyon Consensus criteria for GORD diagnosis: evaluation of conventional and new impedance-pH parameters. *Gut* 2022; 71: 1062–1067.

22. Frazzoni M, de Bortoli N, Frazzoni L, *et al*. Impairment of chemical clearance and mucosal integrity distinguishes hypersensitive esophagus from functional heartburn. *J Gastroenterol* 2017; 52: 444–451.

23. Gao F, Gao Y, Chen X, *et al*. Comparison of esophageal function tests in Chinese patients with functional heartburn and reflux hypersensitivity. *Gastroenterol Res Pract* 2017; 2017: 3596148.

24. Ravi K, Geno DM, Vela MF, *et al*. Baseline impedance measured during high-resolution esophageal impedance manometry reliably discriminates GERD patients. *Neurogastroenterol Motil* 2017; 29: e12974.

25. Hoshikawa Y, Sawada A, Sonmez S, *et al*. Measurement of esophageal nocturnal baseline impedance: a simplified method. *J Neurogastroenterol Motil* 2020; 26: 241–247.

26. Wong MW, Liu TT, Yi CH, *et al*. Analysis of contractile segment impedance during straight leg raise maneuver using high-resolution impedance manometry increases diagnostic yield in reflux disease. *Neurogastroenterol Motil* 2022; 34: e14135.

27. Rengarajan A, Savarino E, Della Coletta M, *et al*. Mean nocturnal baseline impedance correlates with symptom outcome when acid exposure time is inconclusive on esophageal reflux monitoring. *Clin Gastroenterol Hepatol* 2020; 18: 589–595.

28. Ribolsi M, Frazzoni M, Marabotto E, *et al*. Novel impedance-pH parameters are associated with proton pump inhibitor response in patients with inconclusive diagnosis of gastro-oesophageal reflux disease according to Lyon Consensus. *Aliment Pharmacol Ther* 2021; 54: 412–418.

29. Frazzoni L, Frazzoni M, de Bortoli N, *et al*. Postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance can link PPI-responsive heartburn to reflux better than acid exposure time. *Neurogastroenterol Motil* 2017; 29: e13116.

30. Ribolsi M, Savarino E, Rogers B, *et al*. High-resolution manometry determinants of refractoriness of reflux symptoms to proton pump inhibitor therapy. *J Neurogastroenterol Motil* 2020; 26: 447–454.

31. de Bortoli N, Martinucci I, Savarino E, *et al*. Association between baseline impedance values and response proton pump inhibitors in patients with heartburn. *Clin Gastroenterol Hepatol* 2015; 13: 1082–1088.e1081.

32. Gyawali CP, Kahrilas PJ, Savarino E, *et al*. Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; 67: 1351–1362.

33. Sun YM, Gao Y and Gao F. Role of esophageal mean nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave index in discriminating Chinese patients With heartburn. *J Neurogastroenterol Motil* 2019; 25: 515–520.

34. Broeders JA, Draaisma WA, Bredenoord AJ, *et al*. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication. *Br J Surg* 2009; 96: 1023–1030.

35. Aziz Q, Fass R, Gyawali CP, *et al*. Functional esophageal disorders. *Gastroenterology*. Epub ahead of print 15 February 2016. DOI: 10.1053/j.gastro.2016.02.012.

36. Slaughter JC, Goutte M, Rymer JA, *et al*. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2011; 9: 868–874.

37. Zhong C, Liu K, Wang K, *et al*. Developing a diagnostic understanding of GERD phenotypes through the analysis of levels of mucosal injury, immune activation, and psychological comorbidity. *Dis Esophagus* 2018; 31: doy039.

38. Ribolsi M, Guarino MPL, Tullio A, *et al*. Post-reflux swallow-induced peristaltic wave index and mean nocturnal baseline impedance predict PPI response in GERD patients with extra esophageal symptoms. *Dig Liver Dis* 2020; 52: 173–177.

39. Sakin YS, Vardar R, Sezgin B, *et al*. The diagnostic value of 24-hour ambulatory intraesophageal pH-impedance in patients with laryngopharyngeal reflux symptoms comparable with typical symptoms. *United European Gastroenterol J* 2017; 5: 632–640.

40. Chen S, Liang M, Zhang M, *et al*. A study of proximal esophageal baseline impedance in identifying and predicting laryngopharyngeal reflux. *J Gastroenterol Hepatol* 2020; 35: 1509–1514.

41. Doo JG, Kim SI, Park JM, *et al*. Changes in pharyngeal baseline impedance in patients with laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2020; 163: 563–568.

42. Zikos TA, Triadafilopoulos G, Kamal A, *et al*. Baseline impedance via manometry and ambulatory reflux testing are not equivalent when utilized in the evaluation of potential extra-esophageal gastroesophageal reflux disease. *J Thorac Dis* 2020; 12: 5628–5638.

43. Frazzoni M, Frazzoni L, Ribolsi M, *et al*. Applying Lyon Consensus criteria in the work-up of patients with proton pump inhibitory-refractory heartburn. *Aliment Pharmacol Ther* 2022; 55: 1423–1430.

44. Ribolsi M, Frazzoni M, Cicala M, *et al*. Association between post-reflux swallow-induced peristaltic wave index and esophageal mucosal integrity in patients with GERD symptoms. *Neurogastroenterol Motil*. Epub ahead of print 3 March 2022. DOI: 10.1111/nmo.14344.

45. Ates F, Yuksel ES, Higginbotham T, *et al*. Mucosal impedance discriminates GERD from non-GERD conditions. *Gastroenterology* 2015; 148: 334–343.

46. Savarino E, Gemignani L, Pohl D, *et al*. Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2011; 34: 476–486.

47. Galmiche JP, Clouse RE, Bálint A, *et al*. Functional esophageal disorders. *Gastroenterology* 2006; 130: 1459–1465.

48. Rogers B, Samanta S, Ghobadi K, *et al*. Artificial intelligence automates and augments baseline impedance measurements from pH-impedance studies in gastroesophageal reflux disease. *J Gastroenterol* 2021; 56: 34–41.