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Measurement of Esophageal Nocturnal Baseline Impedance: A Simplified Method

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Background/Aims

Mean nocturnal baseline impedance (MNBI) during multichannel intraluminal impedance pH-monitoring (MII-pH) reflects the status of esophageal mucosal integrity. MNBI is suggested as an adjunctive method to distinguish patients with true gastroesophageal reflux disease (GERD) from functional heartburn (FH) and might predict outcomes for anti-reflux treatment. However, current methodology for calculation of MNBI is time-consuming and subject to operator-dependent selection bias. We aim to simplify and provide a more objective method to calculate MNBI.

Methods

We retrospectively analyzed 100 MII-pH tracings from 20 patients with erosive reflux disease, 20 with non-erosive reflux disease (NERD), 20 with reflux hypersensitivity, 20 with functional heartburn (FH), and 20 healthy asymptomatic volunteers. We compared the current "conventional" MNBI analysis with our "simple" MNBI analysis measured by selecting the whole supine period using the impedance average calculation function in the MII-pH software.

Results

Absolute values were very similar and there was a strong correlation between conventional and simple MNBI values in the most distal channel in all groups ($r \geq 0.8$, $P < 0.001$) including patients with increased supine acid reflux. Distal esophageal simple MNBI negatively correlated with acid exposure time ($r = -0.695$, $P < 0.001$). Patients with erosive reflux disease and NERD had lower simple MNBI values in the most distal channel compared to other groups ($P < 0.001$). With a cutoff value of 1785 ohms, simple MNBI can discriminate patients with GERD from those with reflux hypersensitivity and FH (sensitivity 80.0% and specificity 89.7%).

Conclusion

Simple MNBI analysis provides very similar values and has an excellent correlation with conventional MNBI analysis.

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Key Words

Electric impedance; Esophageal mucosa; Esophagitis; Gastroesophageal reflux; Heartburn

Introduction

Esophageal multichannel intraluminal impedance pH-monitoring (MII-pH) is often performed in patients with reflux symptoms to confirm presence of gastroesophageal reflux disease (GERD) when the symptoms are refractory to proton pump inhibitors (PPI) or when endoscopic/surgical interventions are consid-

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ered.[1,2] Although total acid exposure time (AET) is used as a predictive factor for anti-reflux therapies, it has significant day-to-day variability.[1,3-5] In contrast, other parameters from reflux monitoring might be more stable over time and reflect the status of esophageal mucosal integrity.

Measurement of esophageal baseline impedance (BI) reflects esophageal mucosal integrity and correlates well with levels of AET and acid sensitivity.[6-8] Baseline esophageal impedance measurements continuously changes over time due to occurrence of swallows and reflux of liquids and gas. During sleep periods, such changes are minimized. Mean nocturnal baseline impedance (MNBI) was suggested as an accurate method to characterize BI.[9,10] MNBI can distinguish different GERD phenotypes from reflux-unrelated symptoms (functional heartburn [FH]) and provides a good predictive value for anti-reflux therapies.[9-16] However, calculation of MNBI is time-consuming, particularly in patients with supine frequent swallowing and reflux. Furthermore, automatic calculation of MNBI is currently not included in most commercially available MII-pH software. We aim to simplify the method to measure MNBI.

Materials and Methods

Subjects

This was a single-center retrospective case-control study. We analyzed a total of 100 MII-pH tracings obtained from our database at Upper GI Physiology Unit, 20 patients with erosive reflux disease (ERD) (6 grade A, 12 grade B, and 2 grade C), 20 patients with non-erosive reflux disease (NERD), 20 patients with reflux hypersensitivity (RH), 20 patients with FH and 20 healthy asymptomatic volunteers (HV). Eligibility criteria for patients were (1) presence of typical reflux symptoms which were refractory to at least 8-week double dose PPI treatment, (2) an endoscopy performed within 2 years prior to MII-pH, and (3) each group was defined based on Lyon Consensus and Rome IV criteria: ERD diagnosed by an endoscopy, NERD defined as a negative endoscopy and pathological AET (> 6%), RH defined as a negative endoscopy, physiological AET (< 4%), and positive symptom index or symptom association probability, FH defined as a negative endoscopy, physiological AET (< 4%), and negative symptom association probability/symptom index.[1,17] Patients with Barrett's esophagus were excluded. HV did not have relevant medical history, upper abdominal surgery, or pathological reflux at MII-pH investigation. MII-pH measurements were performed between 2017 and 2019 and were re-analyzed as part of this study. Our study adhered to the principles outlined in the Declaration of Helsinki. As this is a retrospective analysis with no identifiable patient data and all tests were performed as clinically indicated, formal ethics approval was not deemed as necessary, but we obtained approval from our Quality and Service Improvement department at Royal London Hospital, Barts Health NHS trust.

Multichannel intraluminal impedance pH-monitoring protocol

Patients were instructed to stop PPI and histamine H2 blocker for at least 7 days prior to the study. After overnight fast, patients underwent High-resolution manometry (Medtronic, Minneapolis MN, USA) to detect the proximal margin of the lower esophageal sphincter (LES) and check the existence and length of a hiatus hernia.[18] Then, we placed the MII-pH catheter (Diversatek Healthcare, Highlands Ranch CO, USA or OMOM, Jinshan Science and Technology, Chongqing, China) with a distal pH sensor at 5 cm above the LES. The catheter has 6 impedance pairs of electrodes at 3, 5, 7, 9, 15, and 17 cm above the LES and 2 pH sensors. We analyzed the MII-pH tracings using the dedicated softwares (Diversatek Healthcare or Jinshan Science and Technology) and visual editing based on our standard protocol.[1,19,20]

Mean nocturnal baseline impedance

We calculated MNBI values in the distal esophagus (at 3 cm and 5 cm above the LES) using 2 methods: "conventional" MNBI reported by Martinucci et al,[9] and a simplified method (simple MNBI). The Chonqing method involved manual measurement of mean BI values at 3 different stable 10-minute time periods (around 1 AM, 2 AM, and 3 AM), excluding reflux episodes and swallowing. Then, the values were averaged to obtain Chonqing MNBI. Simple MNBI was measured during the whole supine period using the automatic calculation function in the software (Fig. 1). If there were 2 or more recumbent period markers, we chose the longest one. These analyses were performed blindly to subjects' conditions.

Data analysis and statistical analysis

All continuous variables are presented as median with interquartile range and assumed not to have a normal distribution. Fisher exact test was used to compare the ratios. Continuous variables were compared using Mann-Whitney *U* test or Kruskal-Wallis test followed by Bonferroni correction for multiple comparisons. Correlation between continuous variables was tested using Spearman's rank correlation test. Diagnostic accuracy of both MNBI values at 5 cm and 3 cm above the LES were assessed using a receiver

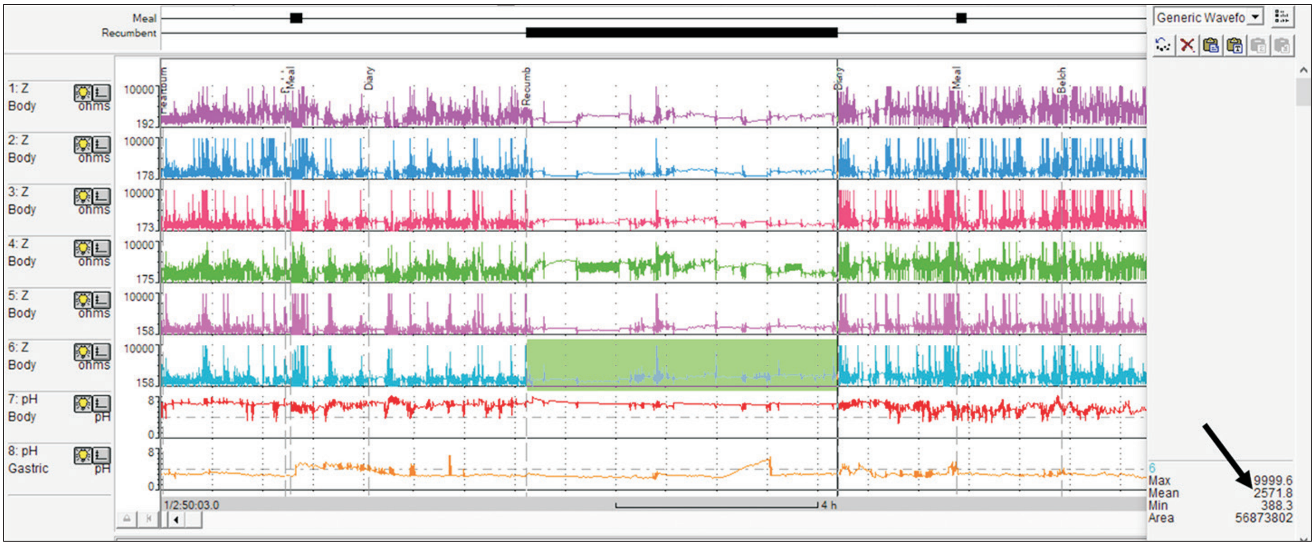

Figure 1. Simple mean nocturnal baseline impedance (MNBI). New method to measure MNBI by selecting whole recumbent period and using the automatic impedance average calculation function provided by commercial software to measure MNBI. The arrow indicates the MNBI value in the most distal channel in this patient.

Table 1. Characteristics of All Groups

Characteristics	ERD (n = 20)	NERD (n = 20)	RH (n = 20)	FH (n = 20)	HV (n = 20)	*P*-value
Age (yr)	56.5 (51.0-64.3)	53.0 (46.8-62.3)	39.0 (35.8-49.8)	43.0 (34.0-51.3)	37.5 (31.0-42.8)	< 0.001
Gender (female)	30%	55%	60%	60%	60%	0.263
BMI	27.0 (24.9-29.7)	26.7 (23.3-28.8)	28.5 (23.0-30.1)	24.6 (22.5-30.0)	ND	0.933
Hiatus hernia	80%	30%	30%	25%	ND	< 0.001
Total acid exposure time (%)	9.6 (7.9-17.2)	8.9 (8.2-11.9)	1.9 (1.1-2.7)	0.7 (0.2-1.6)	0.7 (0.1-1.2)	< 0.001
Upright acid exposure time (%)	13.2 (9.6-16.5)	10.7 (5.8-14.6)	3.2 (1.5-4.8)	1.0 (0.3-2.1)	0.6 (0.2-1.8)	< 0.001
Recumbent acid exposure time (%)	4.1 (0.2-15.9)	7.7 (2.5-13.8)	0.2 (0.0-0.9)	0.2 (0.0-0.5)	0.0 (0.0-0.6)	< 0.001
Total reflux episodes	61.5 (42.8-101.3)	44.0 (32.3-70.0)	47.5 (34.0-55.8)	18.5 (9.8-29.3)	33.0 (20.3-44.8)	< 0.001
Conventional MNBI at 17 cm	2540 (2331-2961)	2639 (1814-3716)	2732 (2389-3263)	2992 (2620-3902)	2169 (1325-3036)	0.186
Conventional MNBI at 15 cm	2030 (1688-2537)	2415 (1445-2810)	2267 (1983-2783)	2680 (2400-3121)	1866 (1027-2434)	0.037
Conventional MNBI at 9 cm	1988 (1481-2383)	1465 (1236-2257)	2222 (1904-2849)	2673 (2193-3196)	2656 (2349-3038)	0.003
Conventional MNBI at 7 cm	1419 (1179-2185)	1460 (1036-2396)	2708 (2297-3159)	3247 (2467-4381)	3094 (2522-4360)	< 0.001
Conventional MNBI at 5 cm	969 (750-1652)	1229 (816-2058)	2867 (2392-3440)	3035 (1692-3152)	2765 (1692-3152)	< 0.001
Conventional MNBI at 3 cm	854 (509-1318)	1370 (812-1773)	2631 (1970-3680)	3200 (2270-4113)	2662 (1971-3344)	< 0.001

ERD, erosive reflux disease; NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; HV, healthy volunteer; BMI, body mass index; MNBI, mean nocturnal baseline impedance; ND, no data.
Value are given as median (interquartile range).

operating characteristics (ROC) analysis. DeLong's test was performed to compare the 2 ROC curves. All statistical analyses were performed with EZR (version 1.36; Saitama Medical Center Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[21]

Results

Patients with ERD and NERD were older than patients with RH, FH, and HV and by definition had significantly higher esophageal acid exposure. Patients with ERD had higher prevalence of hiatus hernia (Table 1). Using conventional MNBI measurements, patients with ERD and NERD showed lower MNBI values than patients with RH, FH, and HV at 3 cm and 5 cm above the LES.

Conventional vs Simple Mean Nocturnal Baseline Impedance

Absolute values of MNBI in the distal esophagus were very similar when calculated using either conventional or simple measurement methods. The median percent difference between absolute values was 11-12%. There was a strong correlation between conventional MNBI and simple MNBI values in all channels among all subjects ($n = 100$, $r \geq 0.8$, $P < 0.001$ in all channels) (Table 2). More importantly, there was a strong correlation between conventional MNBI and simple MNBI values in the most distal impedance channel and this was true for all groups including patients with esophagitis (Table 3). When subjects were divided into those with pathological supine acid exposure (AET > 2.1%)[20] (n = 30) and subjects with normal supine acid exposure (n = 70), we found a very good correlation between conventional and simple MNBI values ($r = 0.96$ and 0.91 respectively, $P < 0.001$ for both).

Both, conventional and simple MNBI values in the distal impedance channel negatively correlated with AET ($r = -0.648$ and -0.695 respectively, $P < 0.001$ for both).

Comparison of Simple Mean Nocturnal Baseline Impedance Values in the Distal Esophagus Among Groups

Table 4 shows simple MNBI median values in all groups. simple MNBI values in the most distal channel showed the same trends as conventional MNBI. Patients with ERD and NERD had significantly lower baseline impedance values than patients with RH, FH, and HV (Fig. 2).

Diagnostic Accuracy of Simple and Conventional Mean Nocturnal Baseline Impedance to Discriminate Patients With Erosive Reflux Disease and "True" Non-erosive Reflux Disease

We assessed accuracy of both methods (measuring MNBI at 5 cm and 3 cm above LES) for diagnosis of GERD (ERD and NERD) using ROC analysis. The area under curves were 0.881 (95% CI, 0.802-0.960) and 0.895 (95% CI, 0.824-0.966) with simple MNBI at 5 cm and 3 cm above the LES respectively, and 0.854 (95% CI, 0.765-0.949) and 0.872 (95% CI, 0.790-0.955) with conventional MNBI. Using a cutoff value of 1785 ohms at 3 cm above the LES, conventional method had a sensitivity of 82.5%

Table 3. Correlation Between Conventional and Simple Mean Nocturnal Baseline Impedance Values in the Most Distal Channel in Each Group

Group	*r*-value	*P*-value
ERD	0.973	< 0.001
NERD	0.967	< 0.001
RH	0.842	< 0.001
FH	0.862	< 0.001
HV	0.886	< 0.001

ERD, erosive reflux disease; NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; HV, healthy volunteer.

Table 2. Correlation Between Conventional and Simple Mean Nocturnal Baseline Impedance Values in All Channels (N = 100)

Channel	Correlation		Absolute values (median)		
	Correlation coefficient	*P*-value	Simple MNBI	Conventional MNBI	*P*-value
At 17 cm	0.85	< 0.001	2698	2671	0.668
At 15 cm	0.80	< 0.001	2295	2332	0.985
At 9 cm	0.86	< 0.001	2155	2270	0.755
At 7 cm	0.90	< 0.001	2311	2461	0.526
At 5 cm	0.95	< 0.001	2304	2350	0.702
At 3 cm	0.95	< 0.001	2258	2193	0.829

MNBI, mean nocturnal baseline impedance.

Table 4. Simple Mean Nocturnal Baseline Impedance Values Among All Groups

Channel	ERD (n = 20)	NERD (n = 20)	RH (n = 20)	FH (n = 20)	HV (n = 20)
Simple MNBI at 17 cm	2529 (2281-2947)	2830 (2016-3424)	2830 (2283-3159)	2987 (2129-3736)	2129 (2016-3424)
Simple MNBI at 15 cm	2198 (1968-2492)	2652 (1890-2882)	2440 (2174-2778)	2641 (1915-3344)	2002 (1193-2121)
Simple MNBI at 9 cm	2010 (1441-2010)	1438 (1198-2027)	2307 (2007-2721)	2582 (2294-3710)	2439 (2152-2984)
Simple MNBI at 7 cm	1446 (1122-1964)	1506 (1043-2174)	2428 (2143-3249)	3019 (2487-4048)	2960 (2454-4055)
Simple MNBI at 5 cm	992 (788-1598)	1192 (854-2153)	2543 (2150-3282)	3127 (2491-3904)	2751 (2269-2943)
Simple MNBI at 3 cm	914 (580-1273)	1276 (801-1797)	2353 (2009-3565)	2932 (2483-4175)	2479 (2055-3167)

ERD, erosive reflux disease; NERD, non-erosive reflux disease; RH, reflux hypersensitivity; FH, functional heartburn; HV, healthy volunteer; MNBI, mean nocturnal baseline impedance.
Value are given as median (interquartile range).

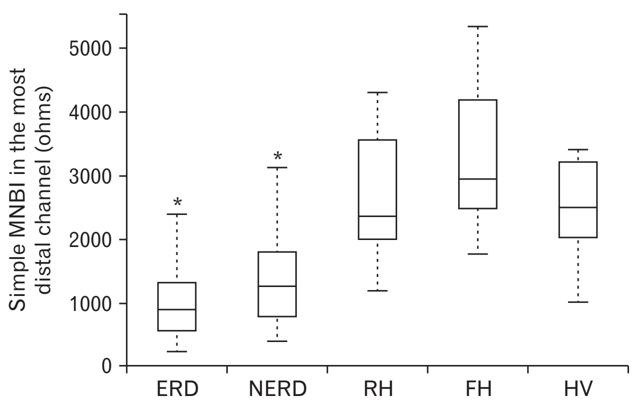

Figure 2. Simple mean nocturnal baseline impedance (MNBI) values in the most distal channel. Patients with erosive reflux disease (ERD) and non-erosive reflux disease (NERD) had lower values than other groups (*$P < 0.001$). RH, reflux hypersensitivity; FH, functional heartburn; HV, healthy volunteer.

and specificity of 89.7%. When measured at 5 cm above the LES, conventional method with a cutoff value of 1943 ohms had a sensitivity of 80.0% and a specificity of 90.0%. Likewise, using a cutoff value of 1785 ohms at 3 cm above the LES, simple MNBI analysis showed a sensitivity of 80.0% and specificity of 89.7%. When calculated at 5 cm, a cutoff value of 2034 ohms had a sensitivity of 80.0% and specificity of 85.0% (Fig. 3).

Table 5 shows there were no significant differences in the proportions of patients who had lower MNBI values than the cutoff with both methods in GERD and non-GERD group.

Discussion

In this study, we have shown that (1) a simplified method to assess baseline impedance during 24 hours reflux monitoring, simple MNBI, correlated very well with the values obtained using the previously described method by Martinucci et al,[9] "conventional" MNBI; a good correlation was found in all patient groups regardless of recumbent acid exposure time, (2) simple MNBI negatively correlated with AET in distal esophageal channels, (3) simple MNBI values were significantly lower in ERD and NERD as compared to patients with FH, RH, and HV, and (4) a cutoff value of 1785 ohms with simple MNBI at 3 cm above the LES can discriminate patients with GERD (ERD and NERD) with sensitivity of 80.0% and specificity of 89.7%.

In our study, we defined the different groups of patients with PPI-refractory typical reflux symptoms using the recent, more stringent criteria suggested by the Lyon Consensus.[1] The current consensus papers and guidelines for GERD management suggest an initial empirical PPI treatment followed by endoscopy and reflux monitoring if the patient does not respond to PPI. Therefore, the group of GERD patient most frequently seen in a tertiary referral center gastrointestinal physiology unit is a patient that was refractory to PPI empirical treatment.

Nevertheless, our simplified method to measure impedance baseline, simple MNBI, showed very similar values and correlations as compared to those from conventional analysis.[7,14] Frazzoni et al[22,23] reported that distal MNBI values in patients with RH is lower than those obtained in patients with FH and suggested that RH patients should be considered as part of the spectrum of reflux disease rather than a functional disorder. Our results did not support a significant difference in the MNBI between the 2 groups in both simple and conventional analysis.

The clinical usefulness of MNBI or BI is still controversial. Some authors suggest that it cannot yet be considered a full diagnostic tool of GERD whereas other authors reported that low BI can be a predictor of outcomes for anti-reflux therapies.[10,15,16,24] In the context of the new definition of GERD provided by the Lyon consensus, Rangarajan et al reported that low MNBI can identify those patients that will respond to anti-reflux therapies if they have a borderline acid exposure ($4\% \leq AET \leq 6\%$).[24] In addition, it

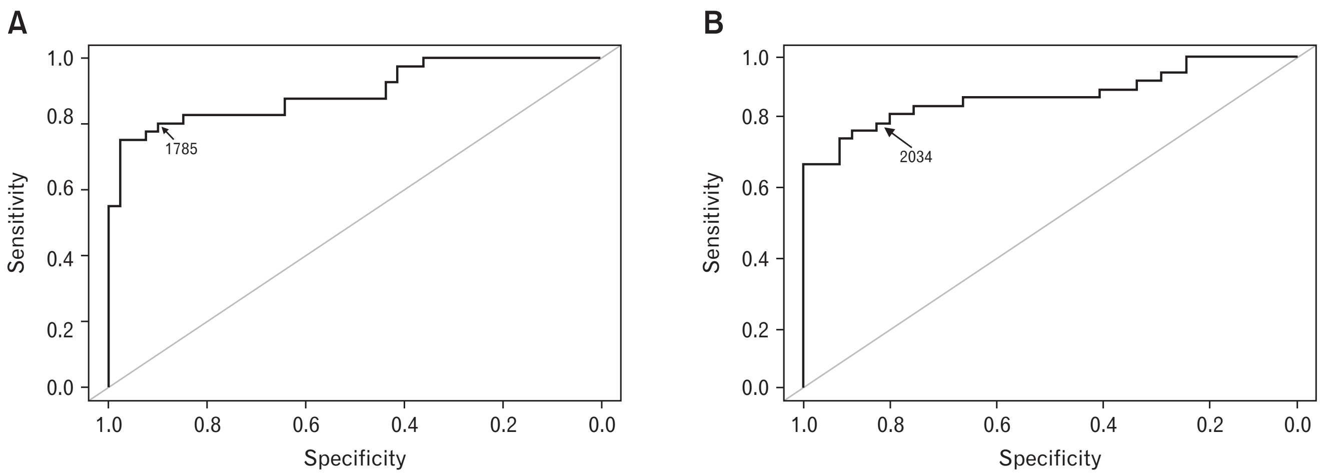

Figure 3. Receiver operating characteristics curves for simple mean nocturnal baseline impedance at 3 cm (A) and 5 cm (B) above the lower esophageal sphincter for diagnosis of gastroesophageal reflux disease. The area under curves were 0.895 (95% CI, 0.824-0.966) and 0.881 (95% CI, 0.802-0.960) respectively, $P = 0.508$.

Table 5. Comparison of the Proportions of Patients Who Had Lower Mean Nocturnal Baseline Impedance Values Than the Cutoff With Both Methods in Gastroesophageal Reflux Disease and Non-gastroesophageal Reflux Disease Groups

Group	MNBI value at 5 cm above the LES			MNBI value at 3 cm above the LES		
	Simple	Conventional	*P*-value	Simple	Conventional	*P*-value
Cutoff value	2034	1943		1785	1784	
Non-GERD (FH + RH)	6/40	4/40	0.737	4/40	4/40	1
GERD (ERD + NERD)	32/40	32/40	1	32/40	33/40	1

MNBI, mean nocturnal baseline impedance; LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease; FH, functional heart burn; RH, reflux hypersensitivity; ERD, erosive reflux disease; NERD, non-erosive reflux disease.

is possible that MNBI could be considered a longitudinal marker of reflux burden, whereas AET has important day-to-day variability.[1,4,8,15] We believe that our simplified method to measure MNBI will facilitate the use of this parameter in further clinical studies.

Our study has limitations. This was a single-center retrospective analysis with relatively small number of subjects yet strong statistical results. We did not compare inter-observer agreement between both analysis methods. It is already known that conventional MNBI analysis has a relatively high interobserver agreement value.[10] In our Center, we use for clinical purpose 2 different MII-pH systems and the clinical data obtained are comparable. We do not have studies using simultaneously the 2 different systems in 1 patient. In any case, the absolute values of MNBI and correlations between the conventional and simple MNBI measurements were similar between the different MII-pH systems.

In summary, our study shows that simple MNBI analysis has an excellent correlation with previously described conventional MNBI analysis. We believe that the new method takes no more than 20 seconds, can prevent a bias and inter-individual variability in selection of periods of analysis, and may prove to be very useful in both clinical and research analysis of MII-pH.

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Conflicts of interest: None.

Author contributions: Yoshimasa Hoshikawa performed analysis of MII tracings, interpretation of the results, and drafting the manuscript; Akinari Sawada, Shirley Sonmez, Kornilia Nikaki, Philip Woodland, and Etsuro Yazaki performed and analyzed the physiology studies; and Daniel Sifrim was involved in design of the study, interpretation of results and drafting of the final manuscript.

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