

Endoscopic-Guided Measurement of Mucosal Admittance can Discriminate Gastroesophageal Reflux Disease from Functional Heartburn

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OBJECTIVES: A novel catheter that can measure mucosal admittance (MA), the inverse of impedance, was developed recently. In this pilot study, we aimed to clarify the usefulness of measuring MA for diagnosing gastroesophageal reflux disease (GERD).

METHODS: We conducted two prospective studies. In the first study, esophageal MA was evaluated in 120 participants (24 with erosive esophagitis, 82 with heartburn but non-erosive esophagitis, and 14 healthy volunteers) and compared with the endoscopic findings. In the second study, multichannel intraluminal impedance combined with pH (MII-pH) tests was conducted followed by an MA measurement in 33 patients with non-erosive esophagitis and proton pump inhibitor (PPI)-refractory heartburn. Based on the MII-pH test results, patients were divided into GERD or functional heartburn (FH). MA was compared between the GERD and FH groups and also compared with the baseline impedance (BI) and acid exposure time (AET).

RESULTS: Median MA at the distal esophagus was significantly higher in patients with erosive esophagitis compared with that in patients with non-erosive esophagitis and healthy volunteers (46.8, 13.1 and 6.5, respectively, $P < 0.01$). In patients with PPI-refractory heartburn, the median MA at the distal esophagus was significantly higher in patients with GERD than those with FH (19.3 vs. 7.2, $P < 0.05$). There was a negative correlation between MA and BI, and a positive correlation between MA and AET at the distal esophagus ($r = -0.46$ and $r = 0.53$, $P < 0.05$).

CONCLUSIONS: Real-time measurement of MA is useful to distinguish GERD from non-GERD.

Clinical and Translational Gastroenterology (2017) 8, e94; doi:10.1038/ctg.2017.22; published online 1 June 2017

Subject Category: Esophagus

INTRODUCTION

Although gastroesophageal reflux disease (GERD) is a common disease worldwide,^{1–3} ~70% of patients with GERD symptoms exhibit no macroscopic evidence of esophageal mucosal injuries. These are termed as either non-erosive reflux disease (NERD) or functional heartburn (FH).⁴ Currently, the multichannel intraluminal impedance test combined with a pH (MII-pH) test is widely used as the gold standard for diagnosing GERD, as it offers high sensitivity and specificity.^{5–8} This test measures both acid reflux and non-acid and gas refluxes. Furthermore, measurement of baseline impedance (BI) in the distal esophagus using the MII-pH test allows prediction of the integrity of the esophageal mucosa in patients with GERD.^{9–15} In addition, BI has been reported to be negatively correlated with esophageal acid exposure time (AET) and is hypothesized to be a marker for microscopic changes in the esophageal mucosa.^{13,15} However, measuring BI using the MII-pH test requires a 24-h testing period and causes considerable patient discomfort.

These limitations led to the development of an endoscopic-guided catheter to measure mucosal impedance (MI).^{16–18}

Ates *et al.*¹⁷ reported that using this catheter, MI measurements could detect GERD with higher levels of specificity and increased positive predictive values than wireless pH monitoring. However, the relationship between MI and BI is uncertain.

Recently, a novel, tiny catheter that can measure mucosal admittance (MA), the inverse of impedance, was developed. This catheter can be fed through the endoscope and used to easily measure MA in real time. The efficacy of admittance measurements using this catheter has been reported previously. In dermatology, it has been used to indicate stratum corneum hydration and the thickness and flexibility of the skin.^{19,20} In the alimentary tract, we reported that MA measured by this catheter inversely correlated with transepithelial electrical resistance of biopsy samples in Ussing chambers.²¹ From these results, we hypothesized that esophageal MA was higher in patients with GERD, and predicted that this easy and real-time evaluation of mucosal permeability during endoscopy could discriminate GERD from non-GERD patients. However, there is no evidence regarding the efficacy of this catheter in diagnosing GERD. Therefore, the main aim of this study was to clarify the efficacy of MA

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Received 30 March 2017; accepted 24 April 2017

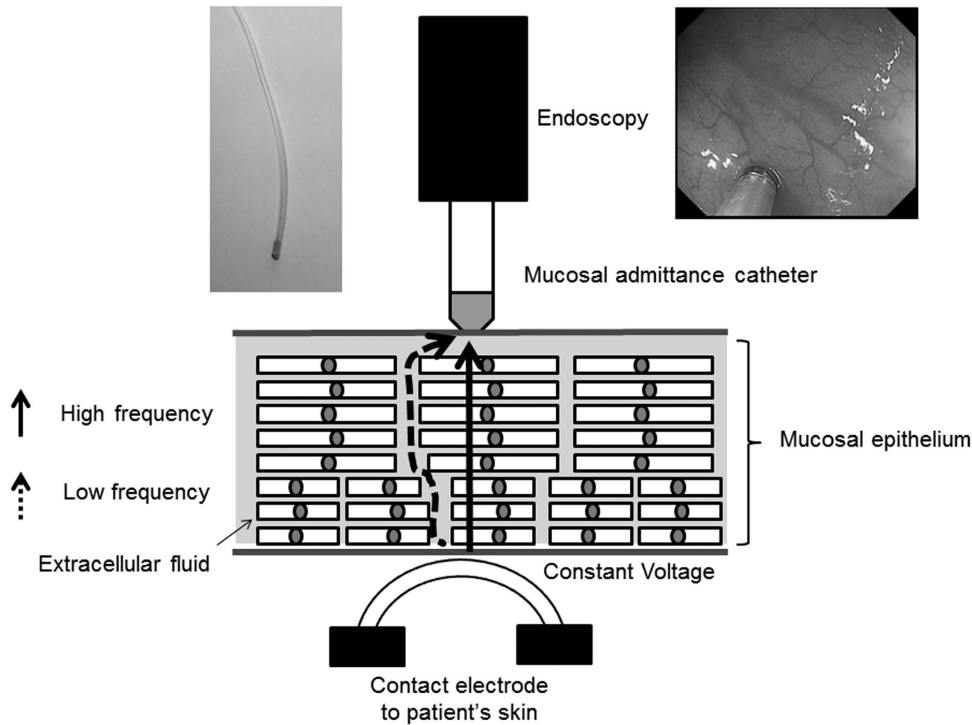


Figure 1 Mucosal admittance (MA) measurements. Schematic representation and photographs of MA catheter. The MA catheter was 1.9 mm in diameter, had an electrode sensor on the tip, and two electrodes attached to the patient's skin. This catheter can be fed through the endoscopy to measure MA by direct mucosal contact in real time.

measurements in diagnosing GERD by (a) comparing the endoscopic findings, (b) comparing between patients with FH and GERD, and (c) measuring the correlation with BI and AET.

METHODS

Study design and participants. This prospective study was conducted in two parts at the Chiba University Hospital (Japan) between April 2015 and November 2016. In the first study, 120 participants (106 patients with heartburn and 14 healthy volunteers) underwent endoscopy, and esophageal MA was measured. Based on the endoscopy results, they were divided into the following groups: erosive esophagitis (EE, $n=24$, 11 with Los Angeles grade A, 9 with Los Angeles grade B, and 4 with Los Angeles grade C), non-EE with heartburn ($n=82$), and non-EE without heartburn (healthy volunteers, $n=14$). MAs were compared with the endoscopic findings. In the second study, 33 patients with non-EE and proton pump inhibitor (PPI)-refractory heartburn underwent MII-pH tests followed by MA measurement. Based on the result of MII-pH tests, they were divided into GERD ($n=16$, 12 with increased AET, and 4 with a normal AET and positive symptom index or symptom association probability) and FH ($n=17$) groups. MAs were compared between FH and GERD, and the correlation with both the BI and AET was measured. PPI-refractory heartburn was defined as present when patients had not responded sufficiently to at least 8 weeks of treatment of PPI. The Frequency Scale in the

Symptoms of GERD questionnaire was used to assess symptom severity.²²

This study was reviewed and approved by the institutional review board of the Chiba University School of Medicine and was registered at the University Hospital Medical Information Network (UMIN000019130). Informed consent was obtained from all participants.

Endoscopic findings. Patients with mucosal breaks identified by endoscopy were classified as having EE based on the Los Angeles classification (grades A–D).⁴

MA measurements. Esophageal MA was measured by two endoscopists (T.M. and H.I.) using a newly developed catheter (TCM: Tissue Conductance Meter, AS-TC100; Asahi Biomed, Tokyo, Japan), which was 1.9 mm in diameter, and had an electrode sensor at the tip, during upper endoscopy²¹ (Figure 1). Reference electrodes were placed on the flexor sides of bilateral forearms. After any liquid visualized during endoscopy was suctioned, the catheter was traversed through the working channel of the endoscope, and the tip was placed on the luminal surface of the mucosa for 2–3 s. Alternating currents of 320 Hz and 30.7 kHz were then loaded at a constant voltage of 12.5 mV. MA was measured five times per location, at points that were 5 cm (distal esophagus) and 15 cm (middle esophagus) above the squamocolumnar junction, avoiding contact with visible changes (no erosions), and the mean values were used for analysis.

MII-pH test. After endoscopy, 24-h MII-pH catheter (Sandhill Scientific, Highland Ranch, CO) was placed after an overnight fast and connected to a ZepHr reflux recording system (Sandhill Scientific) to capture pH, impedance, and symptom data. Patients returned to the hospital the subsequent day for data analysis, which was done using the BioView Analysis Software (Sandhill Scientific) with manual modifications of two experienced investigators (T.M. and H.I.). In our study, 19 out of 33 patients underwent MII-pH testing over 7 days after stopping PPI medication, whereas the remaining 14 who were proven to have GERD on previous investigations (endoscopy and/or MII-pH testing) underwent MII-pH testing while still on PPI therapy. Diagnostic criteria for FH was normal endoscopic appearance of the gastroesophageal junction combined with normal AET (defined as the proportion of time for which pH was <4) without any symptom association (negative symptom index and symptom association probability). Normal AET in patients who had discontinued PPI therapy was defined as lower than 4.2% per day,^{23,24} whereas the definition for patients still taking PPIs was defined as lower than 1.6% in the upright position and 0.6% in the recumbent position.^{25,26} Patients with a normal AET and positive symptom index or symptom association probability have a hypersensitive esophagus and were considered to have a diagnosis of GERD according to the Roma III criteria.²⁷

BI measurements. Esophageal impedance electrodes were located at points that were 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter. BI was assessed at 5 and 15 cm above the lower esophageal sphincter in recumbent patients, as described in previous studies.^{12,13} BI was measured as the mean impedance value during overnight rest, excluding reflux episodes, swallows, and pH drops.^{12,13}

Sample size. The sample sizes for the GERD and FH groups were determined using preliminary data to fit unpaired *t*-test where MA at distal esophagus was the outcome of interest. In this preliminary data, the mean MA was 17.2 and 9.2 in patients with GERD (*n* = 7) and FH (*n* = 7), respectively, and the response within each subject group was normally distributed with a standard deviation (s.d.) of 6.0. If the true difference in the experimental and control means is equal to 9.2, the study would require a sample of 20 patients (10 patients in each group) to be able to reject the null hypothesis (the population means of the experimental and control groups were equal) with a probability of 80% and at a significance

level of 0.05. Assuming a drop rate, we thus aimed to enroll 25 patients with PPI-refractory heartburn.

Statistical analysis. Baseline data have been presented as means ± s.d. Differences in clinical parameter values between groups were analyzed using the unpaired *t*-test, the χ^2 test, Fisher's exact test, or analysis of variance. MA was described using medians and interquartile ranges for continuous variables and proportions for categorical variables. Differences in MA between groups were analyzed using the Mann-Whitney and Kruskal-Wallis tests. Receiver operating characteristic curves were used to summarize the sensitivity and specificity of MA in predicting GERD at all possible cutoff points. The correlations between MA and BI, and MA and AET were analyzed using the Spearman's analysis. All statistical analyses were performed using SPSS 23 (SPSS, Chicago, IL), and a *P* value <0.05 was considered statistically significant.

RESULTS

MA measurements and endoscopic findings. The clinical characteristics of the participants, along with MA at the middle and distal esophagus, are shown in Table 1. The percentage of female patients in non-EE group was significantly higher than EE group and healthy volunteers (*P* < 0.05). The relationship between the endoscopic findings and MA at the distal and middle esophagus is shown in Figure 2. MA at the distal esophagus was significantly higher in patients with EE compared with those without (*P* < 0.01) (Figure 2a). At the middle esophagus, the median MA in patients with EE was significantly higher compared with those with healthy volunteers (*P* < 0.05); however, there was not a statistically significant difference from patients without non-EE (Figure 2b).

24-h MII-pH, MA measurements, and BI measurements. The clinical characteristics of GERD and FH patients, results of the MII-pH test, Frequency Scale in the Symptoms of GERD scores, and the MA and BI levels at the distal and middle esophagus are shown in Table 2. The mean age of FH group was significantly higher compared with the GERD group. There were no significant differences in sex or Frequency Scale in the Symptoms of GERD score between patients with GERD and FH. The MAs at the distal and middle esophagus were significantly higher in patients with GERD compared with those with FH (*P* < 0.05) (Figure 3a,b),

Table 1 Participant characteristics and mucosal admittance at the middle and distal esophagus

	EE, <i>n</i> = 24	Non-EE, <i>n</i> = 82	Healthy volunteer, <i>n</i> = 14	<i>P</i> value
Sex (male/female)	17/7	32/50*	10/4	<i>P</i> < 0.05
Age (years, ± s.d.)	59.3 ± 12.0	56.3 ± 15.8	53.1 ± 17.8	NS
MA at middle esophagus	26.1 (9.3–61.5)**	18.3 (8.3–45.9)	3.3 (1.3–10.8)	<i>P</i> < 0.05
MA at distal esophagus	46.8 (24.3–136.5)***	13.1 (6.9–32.9)***	6.5 (3.9–10.6)	<i>P</i> < 0.01

EE, erosive esophagitis; MA, mucosal admittance; NS, not significant.

*Analysis of variance compared to the EE and the healthy volunteer, *P* < 0.05.

**Kruskal-Wallis test compared with the healthy volunteer, *P* < 0.05.

***Kruskal-Wallis test compared with the healthy volunteer, *P* < 0.01.

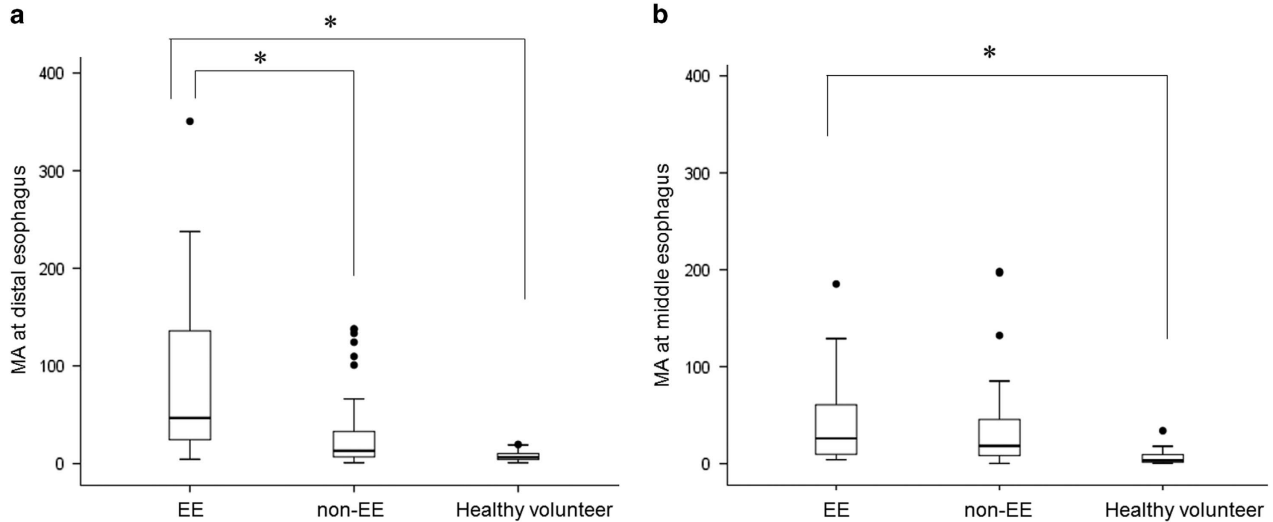


Figure 2 Mucosal admittance (MA) measurements and endoscopic findings. Median MA at (a) the distal esophagus and (b) the middle esophagus for the three study groups, i.e., erosive esophagitis (EE), non-EE with heartburn, and healthy volunteers. The MA at the distal compared with esophagus was significantly higher in patients with EE compared with patients with non-EE and healthy volunteers ($P < 0.01$). At the middle esophagus, the median MA in the patients with EE was significantly higher compared with those with healthy volunteers ($P < 0.05$).

Table 2 Patient characteristics and test results

	GERD, n = 16	FH, n = 17	P value
Sex (male/female)	7/9	7/10	NS
Age (years, \pm s.d.)	66.1 \pm 15.0*	51.6 \pm 17.7	$P < 0.05$
AET	4.7 \pm 3.7**	0.8 \pm 1.0	$P < 0.01$
Total number of refluxes	57.3 \pm 32.8	39.8 \pm 24.1	NS
Acid refluxes	22.0 \pm 17.3	19.9 \pm 16.1	NS
Non-acid refluxes	33.7 \pm 31.3	19.8 \pm 18.1	NS
DeMeester score	15.2 \pm 12.0**	3.2 \pm 3.2	$P < 0.01$
MA at middle esophagus	26.7 (14.1–61.7)**	11.1 (5.1–19.9)	$P < 0.01$
MA at distal esophagus	19.3 (10.2–54.0)*	7.2 (3.9–15.9)	$P < 0.05$
BI at middle esophagus (Ω)	1,741.4 \pm 849.8*	2,827.0 \pm 789.3	$P < 0.05$
BI at distal esophagus (Ω)	1,734.3 \pm 1048.0*	2,849.7 \pm 1201.8	$P < 0.05$
FSSG score	12.5 \pm 7.3	15.8 \pm 7.1	NS

AET, acid exposure time; BI, baseline impedance; FH, functional heartburn; FSSG, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease; GERD, gastroesophageal reflux disease; MA, mucosal admittance; NS, not significant.

* $P < 0.05$.

** $P < 0.01$.

whereas the mean BI level at the same points was significantly lower in patients with GERD compared with those with FH. In patients with GERD, the MAs at the distal and middle esophagus were lower in those with hypersensitive esophagitis than those with abnormal AET (11.0 vs. 30.2 at distal esophagus and 17.6 vs. 32.9 at middle esophagus). However, there were no statistical differences.

Receiver operating characteristic analysis of MA measurements at the distal esophagus for a diagnosis of GERD in

patients with PPI-refractory heartburn at a threshold of 11.0 revealed sensitivity of 68.8%, specificity of 70.6%, positive predictive value of 68.8%, negative predictive value of 70.6%, likelihood ratio positive of 2.33, and likelihood ratio negative of 0.44 (Figure 4a). The corresponding values at the middle esophagus for diagnosis of GERD at a threshold of 13.1 revealed sensitivity of 86.6%, specificity of 64.7%, positive predictive value of 68.4%, negative predictive value of 84.6%, likelihood ratio positive of 2.45, and likelihood ratio negative of 0.21 (Figure 4b).

Correlation between MA and BI. The correlation between MA and BI is shown in Figure 5a,b. A negative correlation was observed between MA and BI at the distal and middle esophagus combined ($r = -0.31$, $P < 0.05$) (Figure 5a). This correlation was stronger at the distal esophagus than at the distal and middle esophagus combined ($r = -0.49$, $P < 0.05$) (Figure 5b).

Correlation between MA and AET. The correlation between MA and AET is shown in Figure 5c. A positive correlation was observed between MA and AET at the distal esophagus ($r = 0.53$, $P < 0.05$).

Complication. There were no complications associated with catheter use.

DISCUSSION

The results of this pilot study suggest that MA measurement using a novel endoscopic-guided catheter may allow the estimation of mucosal integrity, and can also distinguish GERD from FH in a manner similar to 24-h MII-pH monitoring.

The diagnostic tools for GERD have developed rapidly over recent years. At present, the MII-pH test is the gold standard for diagnosing GERD and, by measuring the BI level, mucosal

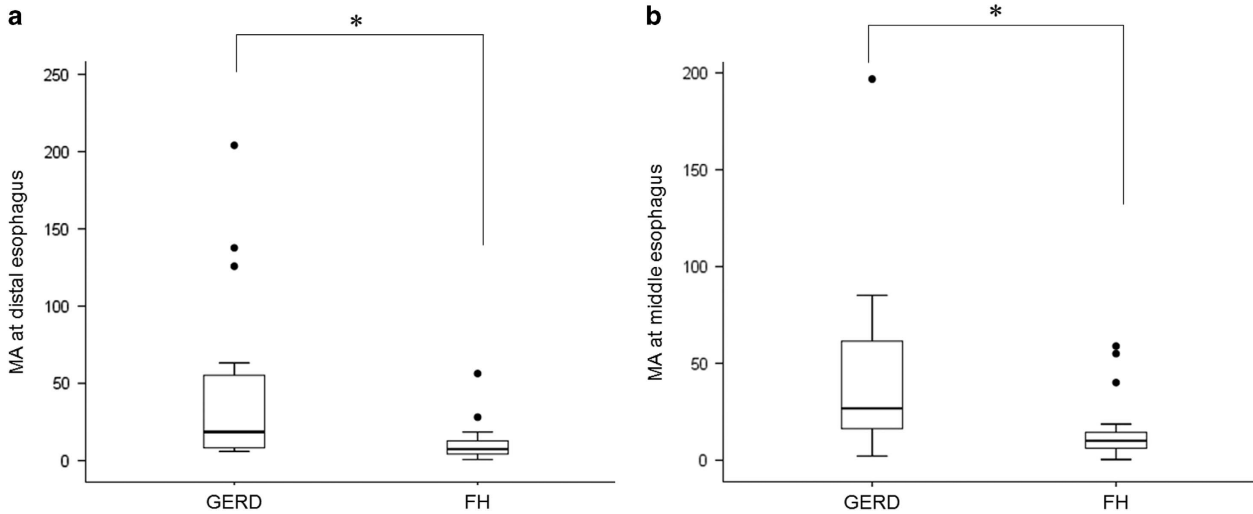


Figure 3 Mucosal admittance (MA) measurements in patients with gastroesophageal reflux disease (GERD) and functional heartburn (FH). (a) The median MA at the distal esophagus was 19.3 in patients with GERD and 7.2 in those with FH. (b) The median MA at the middle esophagus was 26.7 in patients with GERD and 11.1 in those with FH. The MA at the middle and distal esophagus was significantly higher in patients with GERD compared with those with FH ($P < 0.05$).

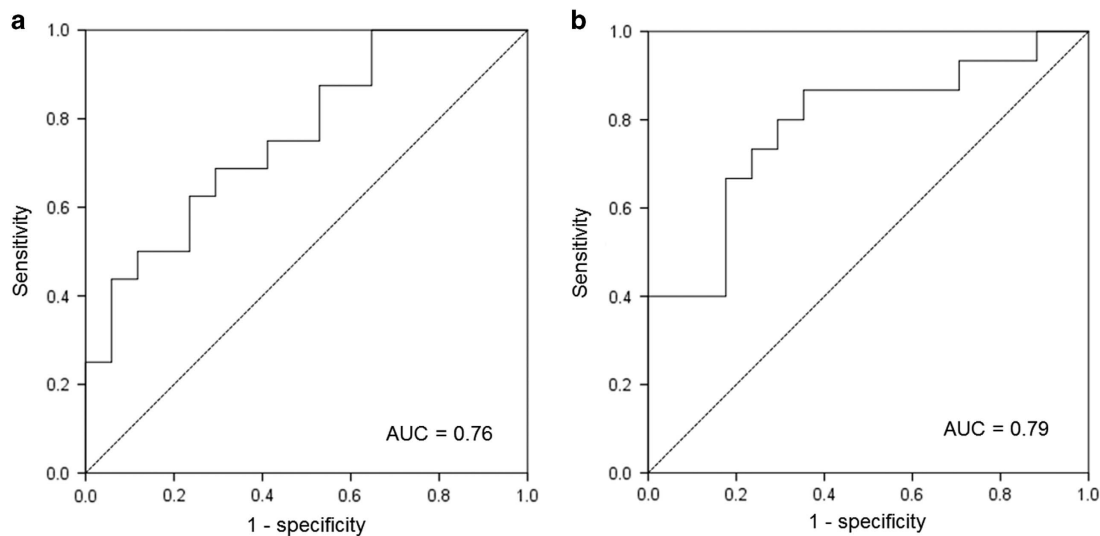


Figure 4 Receiver operating characteristic analysis of mucosal admittance (MA) measurement. (a) Receiver operating characteristic analysis of MA measurement at the distal esophagus for a diagnosis of gastroesophageal reflux disease (GERD) in patients with proton pump inhibitor (PPI)-refractory heartburn at a threshold of 11.0 revealed sensitivity of 68.8%, specificity of 70.6%, positive predictive value of 68.8%, negative predictive value of 70.6%, likelihood ratio positive of 2.3, and likelihood ratio negative of 0.44. (b) The corresponding values at the middle esophagus for a diagnosis of GERD at a threshold of 13.1 revealed sensitivity of 86.6%, specificity of 64.7%, positive predictive value of 68.4%, negative predictive value of 84.6%, likelihood ratio positive of 2.4, and likelihood ratio negative of 0.21.

integrity can be estimated.^{9–15} Farré *et al.*⁹ reported that, in a rabbit model, esophageal transepithelial resistance has a strong negative correlation with dilated intercellular spaces (DIS), and a significant positive correlation with BI. Zhong *et al.*¹³ reported that BI is correlated with esophageal mucosal histopathologic changes such as DIS, and tight junctional protein (claudin-1) in humans. Recently, Yuksel *et al.*¹⁶ and Ates *et al.*¹⁷ reported that an endoscopic-guided catheter can measure MI levels, and this is useful in identifying patients with GERD. In our study, we also showed that the endoscopic-guided MA measurement can distinguish GERD from non-GERD. Because MA is the inverse of MI, our results are

consistent with those of previous studies. The most important difference from the previous reports is that we not only compared the data of patients with GERD and non-GERD but also measured the correlations between MA and BI, and between MA and AET using 24-h MII-pH monitoring. As a result, we determined that there was a significant negative correlation between MA and BI, and a positive correlation between MA and AET. We considered the negative correlation between MA and BI suggests that the MA measurement could estimate mucosal integrity in real time.

There are some differences between the MA measurement of this study and the MI measurement of previous studies.^{16,17}

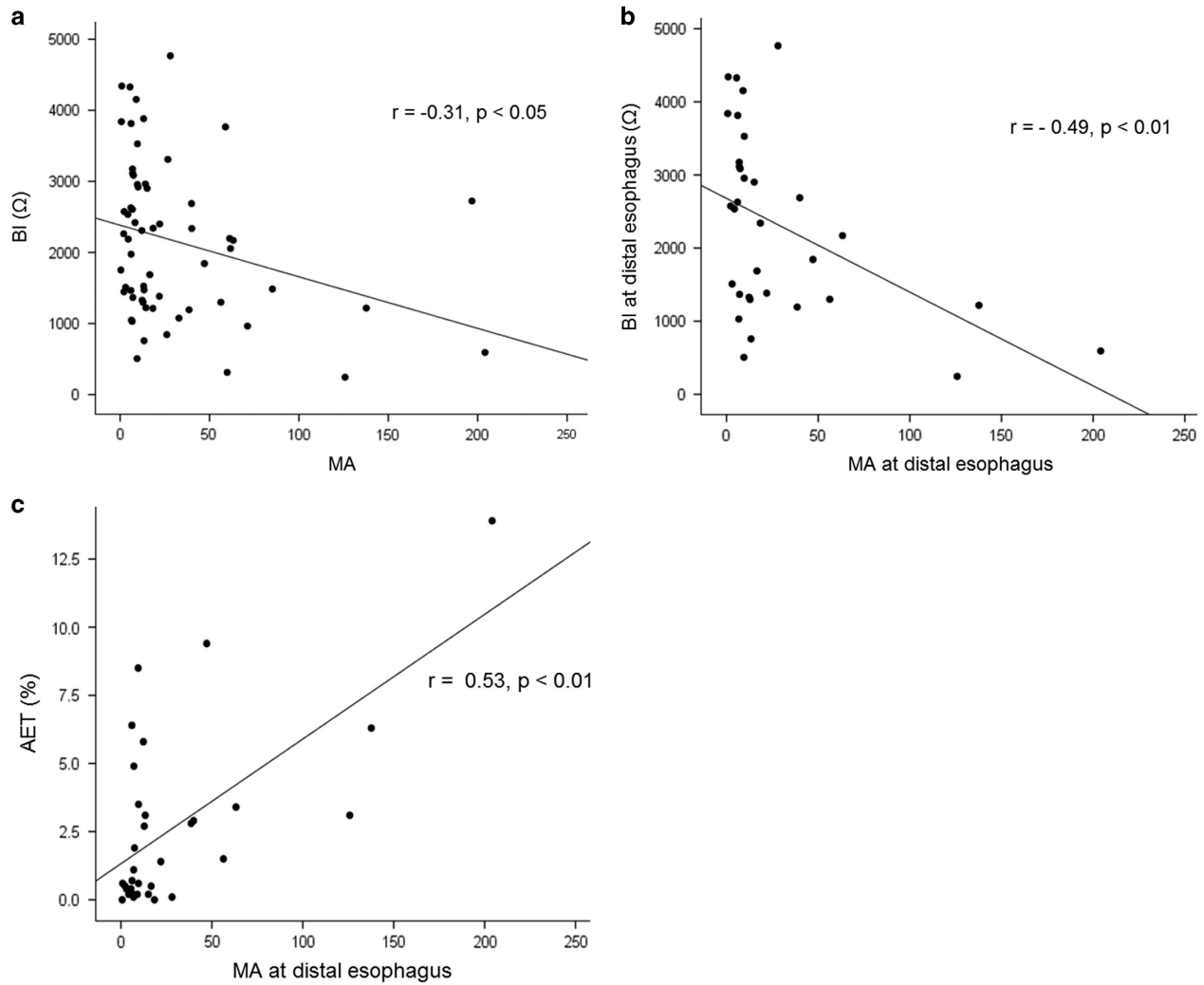


Figure 5 Correlation between mucosal admittance (MA) and baseline impedance (BI), and MA and acid exposure time (AET). (a) Negative correlation was observed between MA and BI at the distal and middle esophagus combined ($r = -0.31$, $P < 0.05$). (b) Negative correlation between MA and BI at the distal esophagus ($r = -0.49$, $P < 0.05$). (c) Positive correlation between MA and AET at the distal esophagus ($r = 0.53$, $P < 0.05$).

The first difference is in the location of the sensor electrode. Conventional MI catheters such as the MII-pH have two parallel circumferential sensors, and the electrical impedance is measured between the two rings. Conversely, the MA catheter has a sensor on the tip; therefore, it can measure MA accurately at a given point in the mucosa. The MI catheter can measure mucosal impedance between its two parallel sensors; therefore, it appears to measure the impedance across the surface of the esophageal mucosa. In other words, mucosal impedance might be strongly affected by the liquid on the epithelium. In contrast, MA was measured through the epithelium by the sensing electrode, suggesting that it can be used to evaluate the full thickness of the esophageal mucosa. Another difference is in the frequencies used. The conventional MI catheter uses one frequency of 2 kHz, whereas the MA catheter uses two frequencies of 30.7 kHz and 320 Hz. Impedance and admittance values vary with contact condition to the epithelium. Using two different frequencies and measuring the differences in flow can exclude

the influence of contact condition to the epithelium. Additionally, the impedance and admittance values of biological tissues are changed by frequencies. In the field of medical engineering, it is widely known that the low-frequency current mostly flows within the extracellular fluid, whereas the high-frequency current flows through intracellular and extracellular spaces; this property is found in all biological tissues.^{28–30} In several functional studies, DIS has been recognized as a marker of impaired transepithelial permeability.^{31,32} Thus, when evaluating extracellular fluid volume, using a low-frequency current may be more useful to estimate DIS and transepithelial permeability. Owing to the above reasons, the MA catheter is considered to be able to evaluate accurately the mucosal condition. In fact, in our previous study, we confirmed that MA inversely correlated with transepithelial electrical resistance of biopsy samples in Ussing chambers.²¹ We are assertive that MA measurement may well become a useful diagnostic tool for patients with GERD.

In our study, in patients with non-EE and PPI-refractory heartburn, MA at the middle esophagus was higher compared with that at the distal esophagus. We considered that the mucosal histopathologic changes of the proximal esophagus might have caused the reflux perception in patients with NERD.

Our study has several limitations. First, the sample size was small. Second, we did not perform histopathological analysis. Therefore, it is uncertain what affected the MA results. Further studies are required to confirm the relationship between MA and histopathological changes such as DIS, esophageal mucosal thickening, and fibrosis. Third, the negative correlation between MA and BI was not strong. This result may have been caused by the difference in the duration of evaluation. BI was evaluated using one 24-h MII-pH test recorded for 1 day, whereas MA was recorded at one point in time. Moreover, several factors, such as food and medication, may also have affected these results. To account for these factors as much as possible, MA was measured just before the MII-pH test. However, it was difficult to exclude entirely the factors. In the present study, although the correlation between MA and BI was not strong, the results may be useful to estimate the BI level and mucosal integrity.

Although our study cohort included a rather small sample size, a cutoff value of 13.14 for MA at the middle esophagus was considered for differentiation between GERD and FH with a sensitivity and specificity of 86.6% and 64.7%, respectively. Therefore, analysis of the MA level can be considered as a useful additional parameter during endoscopy for differential diagnosis of GERD and FH. To the best of our knowledge, this is the first report focusing on the usefulness of MA measurement in diagnosing GERD. Our results indicate that this easy, endoscopic-guided, real-time measurement of MA may be a useful diagnostic tool for patients with GERD.

CONFLICT OF INTEREST

Guarantor of the article: Makoto Arai, MD.

Specific author contributions: Designed the study, conducted the experiment, collected data, analyzed and interpreted data, wrote the manuscript: Tomoaki Matsumura; designed the study, analyzed and interpreted data, assisted in writing the manuscript: Hideaki Ishigami and Makoto Arai; assisted in conducting the experiment and collecting data: Takashi Taida, Shingo Kasamatsu, Kenichiro Okimoto, Keiko Saito, Daisuke Maruoka, and Takeshi Suzuki; designed the study: Tomoo Nakagawa and Tatsuro Katsuno; assisted in interpreting data and writing the manuscript: Mai Fujie. All authors approved the final version of the manuscript.

Financial support: None.

Potential competing interests: None.

Acknowledgments. We thank Dr Takeo Odaka (Odaka Medical and Gastrointestinal Clinic, Chiba, Japan) for helping plan the project. In addition, we also thank the study participants for their contribution.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Approximately 70% of patients with gastroesophageal reflux disease (GERD) symptoms exhibit no macroscopic evidence of mucosal injuries.
- ✓ The standard method of distinguishing non-erosive reflux disease (NERD) from functional heartburn (FH) requires 24-h MII-pH monitoring.
- ✓ Endoscopic-guided measurement of mucosal impedance has been reported to be useful for diagnosing GERD.

WHAT IS NEW HERE

- ✓ Endoscopic-guided measurement of mucosal admittance (MA) could estimate mucosal integrity.
- ✓ Measurement of mucosal admittance could distinguish GERD from FH similar to a 24-h MII-pH monitoring.

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