



# Mucosal Impedance Discriminates GERD From Non-GERD Conditions

Fehmi Ates,<sup>1</sup> Elif Saritas Yuksel,<sup>1</sup> Tina Higginbotham,<sup>1</sup> James C. Slaughter,<sup>2</sup> Jerry Mabary,<sup>3</sup> Robert T. Kavitt,<sup>1</sup> C. Gaelyn Garrett,<sup>4</sup> David Francis,<sup>4,5</sup> and Michael F. Vaezi<sup>1</sup>

<sup>1</sup>Division of Gastroenterology, Hepatology and Nutrition and <sup>2</sup>Department of Biostatistics, Vanderbilt Medical Center, Nashville, Tennessee; <sup>3</sup>Sandhill Scientific Inc, Denver, Colorado; and <sup>4</sup>Vanderbilt Voice Center and <sup>5</sup>Center for Surgical Quality and Outcomes Research, Vanderbilt Institute for Medicine & Public Health, Nashville, Tennessee

Podcast interview: [www.gastro.org/gastropodcast](http://www.gastro.org/gastropodcast). Also available on iTunes. See editorial on page 282.

**BACKGROUND & AIMS:** Current diagnostic tests for gastroesophageal reflux disease (GERD) are suboptimal and do not accurately and reliably measure chronicity of reflux. A minimally invasive device has been developed to assess esophageal mucosal impedance (MI) as a marker of chronic reflux. We performed a prospective longitudinal study to investigate MI patterns in patients with GERD and common nonreflux conditions, to assess MI patterns before and after treatment with proton pump inhibitors and to compare the performance of MI and wireless pH tests. **METHODS:** We evaluated MI in 61 patients with erosive esophagitis, 81 with nonerosive but pH-abnormal GERD, 93 without GERD, 18 with achalasia, and 15 with eosinophilic esophagitis. MI was measured at the site of esophagitis and at 2, 5, and 10 cm above the squamocolumnar junction in all participants. MI was measured before and after acid suppressive therapy, and findings were compared with those from wireless pH monitoring. **RESULTS:** MI values were significantly lower in patients with GERD (erosive esophagitis or nonerosive but pH-abnormal GERD) or eosinophilic esophagitis than in patients without GERD or patients with achalasia ( $P < .001$ ). The pattern of MI in patients with GERD differed from that in patients without GERD or patients with eosinophilic esophagitis; patients with GERD had low MI closer to the squamocolumnar junction, and values increased axially along the esophagus. These patterns normalized with acid suppressive therapy. MI patterns identified patients with esophagitis with higher levels of specificity (95%) and positive predictive values (96%) than wireless pH monitoring (64% and 40%, respectively). **CONCLUSIONS:** Based on a prospective study using a prototype device, measurements of MI detect GERD with higher levels of specificity and positive predictive values than wireless pH monitoring. [ClinicalTrials.gov](http://ClinicalTrials.gov), Number: NCT01556919.

implications and a substantial economic burden.<sup>3–5</sup> The annual direct cost for management of GERD is estimated at \$971 per patient, with projected national expenditures ranging from \$9.3 billion to \$12.1 billion.<sup>3,6,7</sup> Compounding these growing expenditures is the increasing prevalence of partial responders or nonresponders to empiric acid suppressive therapy. Patients with GERD often undergo diagnostic esophageal pH tests using intraluminal esophageal probes, but this technology has largely remained static since initially designed in the 1970s.<sup>8,9</sup>

Current diagnostic tests for GERD are suboptimal because they lack adequate sensitivity or specificity and only detect reflux if it occurs during the test period. Therefore, patients with reflux who do not have adequate events during the test have falsely negative results, often leading to alternative diagnoses and improper treatment.<sup>10,11</sup> The current armamentarium of diagnostic modalities for GERD includes several options with variable utility. For example, esophageal erosion identified on esophagogastroduodenoscopy (EGD) is highly specific for GERD. However, it lacks sensitivity because less than 30% of affected patients exhibit erosive disease. Furthermore, endoscopic scoring of “mild” disease is subjective and not very reliable.<sup>12</sup> Moreover, many presenting patients have normal-appearing mucosa at endoscopy given the widespread use of acid suppressive agents.

Ambulatory pH and intraluminal impedance monitoring is the current gold standard; however, it is limited because it can only measure reflux activity during the 24- to 48-hour testing period, which is affected by variable patient compliance with “routine daily activity” as a result of catheter discomfort and altered daily routine.<sup>13–15</sup> These ambulatory reflux monitoring devices have acceptable sensitivity (77%–100%) and specificity (85%–100%) in patients with endoscopic esophagitis but are less sensitive (0%–71%) among endoscopy-negative patients.<sup>10,11</sup> Furthermore, these

**Keywords:** PPI; Reflux Damage; Comparative Analysis.

Gastroesophageal reflux disease (GERD) occurs when reflux of gastroduodenal contents causes troublesome symptoms and/or complications.<sup>1</sup> GERD is estimated to affect 20% to 30% of the population in Western countries<sup>2</sup> and is associated with major quality-of-life

**Abbreviations used in this paper:** DIS, dilated intercellular spaces; E+, erosive esophagitis; E−/pH+, nonerosive mucosa with abnormal pH; E−/pH−, nonerosive mucosa with normal pH; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; IQR, interquartile range; MI, esophageal mucosal impedance; PPI, proton pump inhibitor; SCJ, squamocolumnar junction.

tests determine the presence of reflux but do not measure the long-term mucosal consequences of GERD, which is a significant limitation of existing platforms.

Recently, the presence of dilated intercellular spaces (DIS) in the esophageal mucosa as seen on transmission electron microscopy of biopsy specimens has been suggested as a marker of chronicity of GERD in patients with either esophagitis or nonerosive reflux disease.<sup>16-18</sup> In animal models, DIS is a consequence of acid-peptic injury to the apical surface of the epithelial cells and of acute stress, which increases paracellular permeability across the epithelial layers and likely allows diffusion of H<sup>+</sup> ions into the intercellular space.<sup>19-21</sup> Therefore, H<sup>+</sup> access to sensory nerve endings in the mucosa might account for the symptoms occurring in patients without mucosal breaks.<sup>22</sup> Despite these promising findings, the role of DIS in the diagnosis of GERD remains unknown due to uncertainty regarding optimal biopsy site, the need for expensive and not widely available transmission electron microscopy, and recent contradictory findings.<sup>23</sup>

Measurement of esophageal intraluminal impedance recently has suggested lower intraluminal impedance values for patients with GERD compared with controls.<sup>24</sup> However, this finding is based on traditional catheter-based 24-hour ambulatory measurements. This technology uses indirect mucosal conductivity measurements at a fixed location along the esophagus and is hampered by patient discomfort. The intraluminal impedance measurements are indirect, with uncertainty of direct mucosal contact. In addition, these measurements are associated with suboptimal sensor array and impedance rings that are too far apart (typically 1.6 cm). Finally, there is less certainty as to whether the measurements are influenced by intraluminal contents, which by design cannot be excluded, resulting in inherent measurement errors.

We recently developed and validated a minimally invasive, simple, and low-cost device to assess changes in esophageal mucosal impedance (MI) as a tool to measure the presence and chronicity of reflux.<sup>25</sup> The aims of this prospective longitudinal study were to (1) investigate MI patterns in patients with GERD and common nonreflux conditions to assess test characteristics, (2) assess MI patterns before and after proton pump inhibitor (PPI) therapy in patients with GERD, and (3) compare the performance of MI and wireless pH testing.

## Patients and Methods

This study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. Each patient signed a consent form before undergoing any study-related procedures. The Vanderbilt Institutional Review Board approved this clinical trial (IRB# 101109; NCT01556919). All authors had access to the study data and reviewed and approved the final manuscript.

### Patient Population and Study Design

The study population consisted of patients with upper gastrointestinal symptoms referred for diagnostic testing for GERD and those with eosinophilic esophagitis (EoE) and

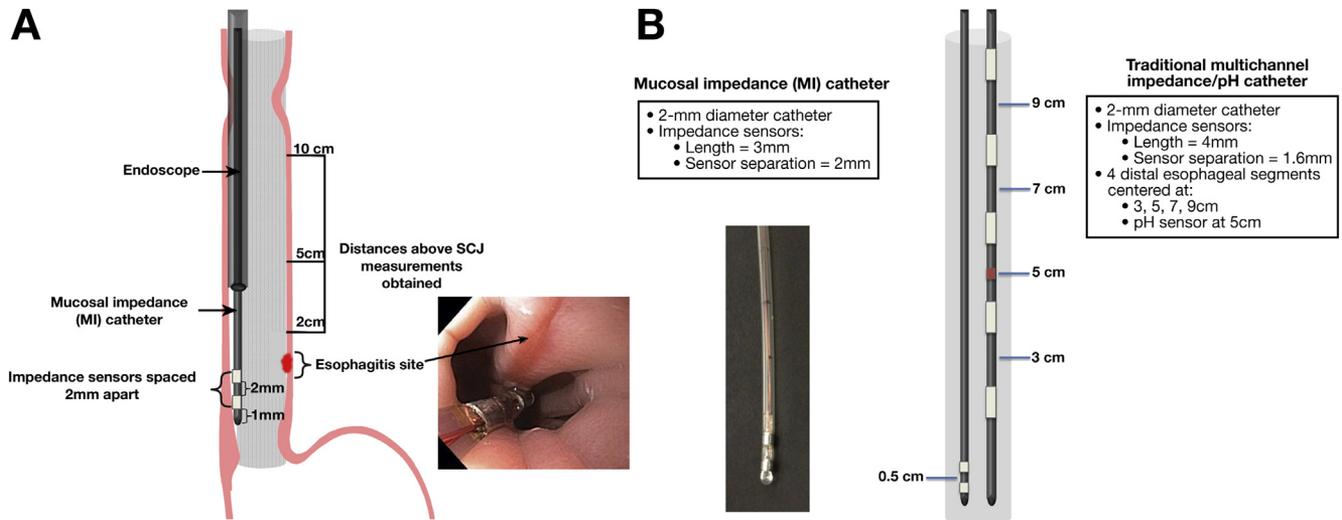
achalasia. Reflux testing was conducted to (1) confirm reflux in those with complete response to PPI therapy before surgical fundoplication (22%) or (2) confirm esophageal acid exposure in those with an incomplete response to acid suppressive therapy as part of a workup to assess for GERD as the cause of symptoms (78%). Presenting symptoms in the former group included heartburn, regurgitation, epigastric pain, chronic cough, laryngitis, and asthma. Patients were excluded from the study if they had Barrett's esophagus, had a history of esophageal surgery or gastrointestinal cancer, had peptic ulcer disease, or did not discontinue the use of PPIs 10 days before endoscopy and histamine receptor antagonists 7 days before endoscopy. Patients with confirmed EoE had dysphagia, a ringed esophagus, and histological confirmation (>15 eosinophils per high-power field in both distal and proximal esophageal biopsy specimens). pH testing was not conducted in patients with EoE because it is not included in the current recommendations for initial evaluation of these patients.<sup>26</sup> Patients with achalasia had dysphagia to solids and liquids, endoscopic features of mild to moderate dilation of the esophagus with retained saliva and food as well as a puckered gastroesophageal junction, and manometric confirmation with esophageal aperistalsis and partial or poor relaxation of the lower esophageal sphincter. Patients with achalasia served as an important second control group for comparison between the divergence of impedance measurements based on direct mucosal contact (MI) and intraluminal measurements.

All participants underwent EGD. Wireless pH testing was performed to measure the degree of esophageal acid exposure in all patients being evaluated for GERD (excluding achalasia and EoE). Before placement of the wireless pH capsule, the MI catheter was traversed through the working channel of the endoscope and direct contact MI measurements were obtained by touching the MI sensors to the esophageal lining. Any liquid visualized during endoscopy was suctioned before measurement of MI to minimize confounding. Measurements were taken at 2, 5, and 10 cm above the squamocolumnar junction (SCJ) relative to the lesser curvature of the stomach and directly measured at the site of eroded mucosa if there was evidence of erosive esophagitis (Figure 1A). MI measurements were obtained continuously for 5 seconds at each location, and the mean measurement for each location was used for analysis. MI measurements were recorded without knowledge of the wireless pH results.

Patients were divided into 5 groups based on clinical presentation, endoscopic, and pH monitoring data: (1) erosive esophagitis (E+), (2) nonerosive mucosa with abnormal pH (E-/pH+), (3) nonerosive mucosa with normal pH (E-/pH-), (4) EoE, and (5) achalasia. The first 2 groups represented those with objective GERD, and the latter 3 groups constituted the non-GERD group. MI values for groups were compared with each other and at different levels along the esophageal axis (Figure 1A). EGD and MI measurements were repeated in patients discovered to have LA grade C or D esophagitis on index endoscopy after treatment with PPIs for 6 to 8 weeks to assess the effect of therapy on esophageal inflammation as well as MI pattern.

### Measurement of MI

A newly designed MI catheter (Figure 1B) was engineered to measure electrical impedance of the esophageal lining by direct mucosal contact. A special sensor array composed of 360° circumferential sensing rings (Sandhill Scientific Inc,



**Figure 1.** Schematic representation of MI catheter. (A) Two 2-mm-long impedance sensing electrodes positioned 1 mm from the tip of a 2-mm soft catheter were advanced through an upper endoscope. MI measurements were obtained by direct mucosal contact of sensors at the site of esophagitis (if present) and 2, 5, and 10 cm above the SCJ. (B) Photograph of the MI catheter (*inset*) and schematic comparison of the MI catheter to the traditional multichannel impedance pH catheter along the esophageal lumen. Measurements represent distances from the SCJ.

Denver, CO) was engineered and mounted on a catheter 2 mm in diameter (Figure 1B) with the following specifications: (1) ring length of 3 mm, (2) ring separation of 2 mm, (3) end of distal ring mounted 1 mm away from the tip of the catheter, and (4) a soft catheter easily traversable through the working channel of an upper endoscope. The electrodes were connected to an impedance voltage transducer at the bedside via thin wires, which ran the length of the catheter. The voltage generated by the transducer was limited to produce at most 10  $\mu$ A of current. The frequency for the measuring circuit was set at 2 kHz. Impedance measurements of the esophageal mucosa were expressed in ohms as the ratio of voltage to the current. Data were acquired with a stationary impedance data acquisition system (InSight; Sandhill Scientific Inc) and were viewed and analyzed by using BioView Analysis software (Sandhill Scientific Inc). Unique specifications for the new catheter relative to the traditional multichannel esophageal impedance/pH catheter are highlighted in Figure 1B.

### Wireless pH Monitoring

Ambulatory pH monitoring was performed for 48 hours using Bravo wireless pH monitors (Given Imaging, Duluth, GA). Wireless capsules were calibrated by submersion in buffer solutions at pH 7.0 and pH 1.0 and then activated by magnet removal. Patients underwent EGD with deep sedation (ie, propofol) for visual anatomic inspection and collection of distance measurements from the incisors to the SCJ. Wireless pH capsules then were placed as previously described.<sup>27</sup> Measurements of the total, upright, and supine percentage time when esophageal pH was <4 were determined over day 1 and day 2 of the wireless pH study. Acid exposure time (percent time pH was <4) greater than 5.3% per day was considered abnormal.<sup>28</sup>

### Statistical Analysis

Data were collected and stored in the secure web-based Vanderbilt Digestive Disease Center REDCap database (Research Electronic Data Capture) (1 UL1 RR024975 NCR/

National Institutes of Health). There was strict control and supervision of data entry and access to study data.

Patient characteristics were described using medians and interquartile ranges for continuous variables and proportions for categorical variables. Statistical differences in outcomes among groups and different esophageal sites were assessed using the Kruskal-Wallis test or the Pearson  $\chi^2$  test. Receiver operating characteristic curves were used to summarize the sensitivity and specificity of MI to predict GERD at all possible cutoff points. The area under the receiver operating characteristic curve was estimated with a 95% confidence interval to evaluate the predictive accuracy of MI. Hypothesis tests were considered significant if the *P* value was  $\leq .05$ . The positive predictive value of MI measurements was then compared with pH monitoring in diagnosing GERD. In the subset of patients in whom MI was measured both before and after PPI therapy, pre-MI and post-MI values at each location were compared using paired *t* tests. Separate logistic regression models were used to estimate the probability of esophagitis as a function of MI and total percent time pH was <4. MI and total percent time pH was <4 were included as continuous covariates in each model.

## Results

### Demographics

A total of 268 patients were studied and stratified into those with E+ (*n* = 61) (LA grade A, 28; grade B, 18; grade C, 10; and grade D, 5), E-/pH+ (*n* = 81), E-/pH- (*n* = 93), achalasia (*n* = 18), and EoE (*n* = 15) (Table 1). As expected, patients with EoE were younger than those in other groups; in addition, like patients with achalasia, patients with EoE were mostly male (*P* < .001) and had significantly more dysphagia as the presenting symptom than those in other groups (*P* < .001). There were no other differences in patient characteristics or presenting symptoms among the groups. Patients with GERD (E+ and E-/pH+ groups) had

**Table 1.** Demographic Data of the Study Population

	E+ (n = 61)	E-/pH+ (n = 81)	E-/pH- (n = 93)	Achalasia (n = 18)	EoE (n = 15)	P value
Age (y)	50 (39–62)	54 (46–63)	54 (44–63)	55 (34–59)	35 (33–45)	<.001
Sex (% male)	38	33	22	85	98	<.001
Race (% white)	87	82	75	77	100	.33
Body mass index (kg/m <sup>2</sup> )	30 (27–32)	28 (26–33)	26 (23–34)	30 (24–32)	37 (30–38)	.03
Symptoms (%)						
Heartburn/regurgitation	80	71	69	5	4	.001
Chronic cough	10	22	15	0	0	
Hoarseness	0	2	4	0	0	
Throat clearing	0	3	5	0	0	
Dysphagia	10	2	7	95	96	
Time pH <4 (%)						
Total	11.4 (6.4–13.5)	8.6 (5.2–11.8)	1.7 (0.6–2.9)	—	—	<.001
Upright	12.5 (7.6–17.2)	10.7 (7.1–14.4)	2.7 (0.8–4.2)	—	—	<.001
Supine	7.7 (2.1–17.8)	3.8 (0.9–8.3)	0.1 (0.0–0.5)	—	—	<.001

NOTE. Values are median (IQR) or percent.

significantly ( $P < .001$ ) greater acid reflux exposure (total, upright, and supine percent time pH was <4) than those without GERD (E-/pH- group) (Table 1).

## MI

**Group differentiation.** Overall, median (interquartile range [IQR]) MI measurements ( $\Omega$ ) were significantly ( $P < .001$ ) lower for the GERD and EoE groups than the non-GERD groups (Figure 2A–C) (Table 2). The pattern of MI values along the esophagus was unique for those with GERD (E+, E-/pH+), non-GERD (E-/pH-, achalasia), and EoE (Figure 2D). In GERD and non-GERD patients, there was a numerical increase in MI measurements from the distal to proximal esophagus (Figure 2D), with the lowest measurements at the site of mucosal erosion (esophagitis) (775  $\Omega$  [613–1042  $\Omega$ ]), followed in order by 2, 5, and 10 cm above the SCJ. Median (IQR) MI measurements ( $\Omega$ ) were similar ( $P = .7$ ) among those with GERD (E+, E-/pH+) and at all esophageal sites were significantly ( $P < .001$ ) lower from those without GERD (E-/pH-, achalasia) (Figure 2D). The MI pattern was unique in patients with EoE, showing low median (IQR) MI measurements all along the esophagus (2, 5, and 10 cm above the SCJ) with values that did not exceed 2000  $\Omega$ . Patients with endoscopic grade A and B esophagitis had significantly ( $P = .01$ ) higher median (IQR) MI values (903 [610–1055]) than those with grade C and D esophagitis (376 [278–702]). There was no difference ( $P = .6$ ) in baseline MI values for patients with esophageal or extraesophageal symptoms. The median (IQR) MI values ( $\Omega$ ) at 2 and 5 cm were lower ( $P = .11$ ) in patients who underwent testing before fundoplication (1616 [1053–2042] and 2319 [1712–2800], respectively) than in those who were evaluated for partial response to PPI therapy (1850 [1200–2960] and 2450 [1534–3900], respectively).

**Test characteristics.** Receiver operating characteristic analysis of MI measurements at 2 cm above the SCJ for diagnosis of objective GERD (abnormal pH and/or esophagitis) at a threshold of 1465  $\Omega$  revealed sensitivity of 70%, specificity of 91%, positive predictive value of 89%, and negative predictive value of 68% with positive and

negative likelihood ratios of 6.98 and 0.43, respectively (Table 3). Thus, at 2 cm above the SCJ, those with objective reflux were 6.98 times more likely to have an MI measurement less than 1465  $\Omega$  than non-GERD patients and nearly half as likely to have values above this threshold. At 5 cm above the SCJ, the optimal MI threshold was calculated to be 2019  $\Omega$ , yielding sensitivity of 76%, specificity of 95%, positive predictive value of 96%, and negative predictive value of 69% with positive and negative likelihood values of 12.1 and 0.38. Thus, at 5 cm above the SCJ, those with objective reflux were 12.1 times more likely to have MI measurement values less than 2019  $\Omega$  than non-GERD patients and less than half as likely to have values above this threshold.

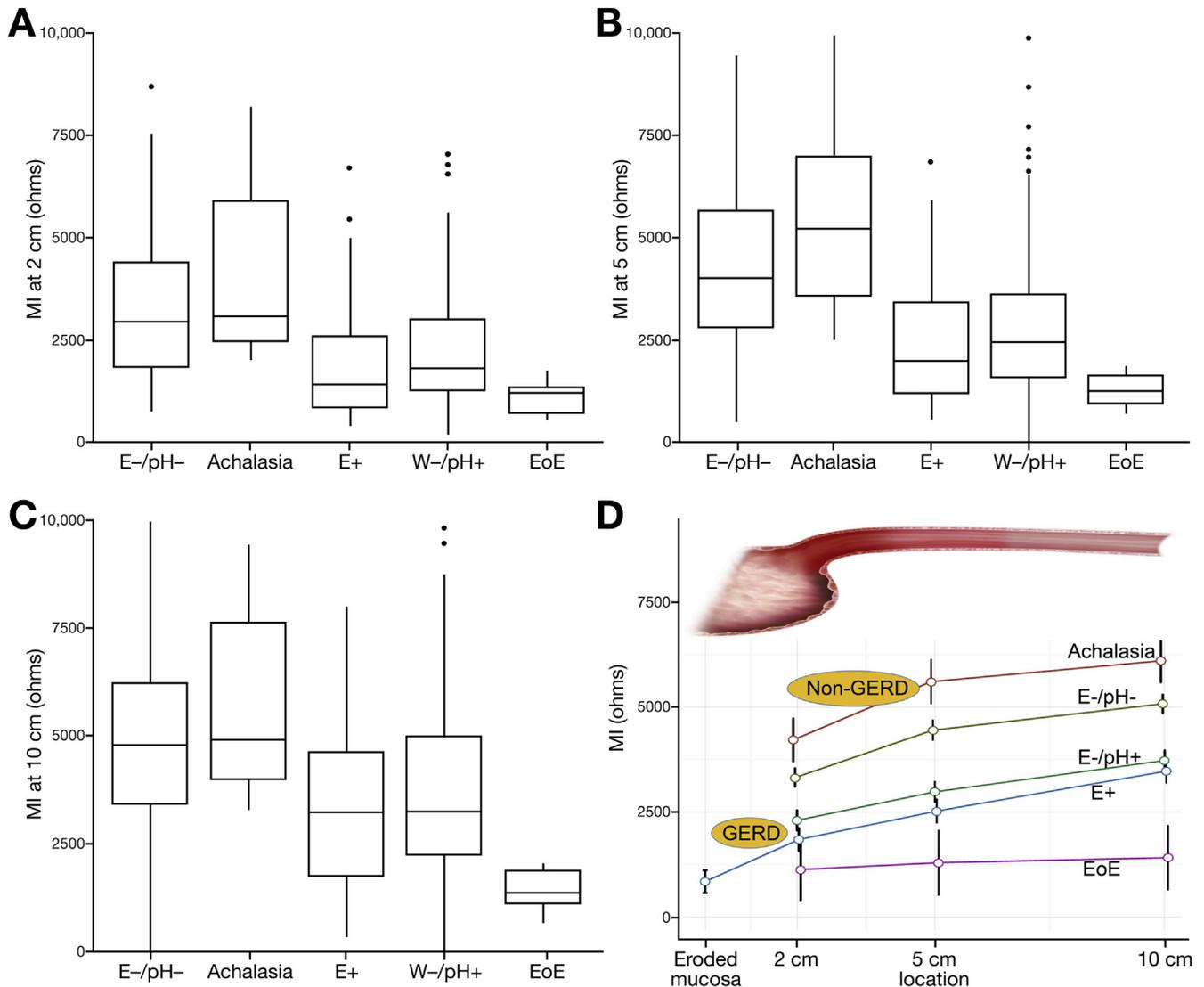
**Before and after PPI therapy.** Among patients with erosive esophagitis, baseline MI values significantly ( $P < .001$ ) increased after PPI therapy at all 3 esophageal locations (Figure 3). Means of the differences were 2491  $\Omega$  at 2 cm, 1728  $\Omega$  at 5 cm, and 2738  $\Omega$  at 10 cm above the SCJ.

**MI compared with wireless pH.** Considering esophagitis as the most objective criteria for GERD, predictive probabilities were determined based on pH and MI measurements. For pH monitoring, there was no pH cutoff at which the probability of esophagitis increased sharply; for MI, the predictive probability of esophagitis sharply increased at MI values less than 2000  $\Omega$  (Figure 4A and B). Based on this model, MI had superior specificity and positive predictive values (95% and 96%, respectively) compared with pH monitoring (64% and 40%, respectively). The sensitivity and negative predictive values were similar between the groups at 76% and 69%, respectively, for MI and at 75% and 72%, respectively, for pH monitoring.

There were no complications associated with MI catheter use, and it added an average of 2 minutes to the time needed to perform endoscopy.

## Discussion

In this prospective study, we showed the clinical performance of an innovative MI measurement device in



**Figure 2.** Median (IQR) MI measurements at (A) 2 cm, (B) 5 cm, and (C) 10 cm above the SCJ for the 5 study groups. MI measurements were significantly ( $P < .001$ ) lower for GERD (E+, E-/pH+) and EoE than non-GERD (achalasia or E-/pH-). (D) Median (IQR) MI values in an axial distribution along the esophagus for the 5 study groups. GERD and non-GERD patients showed lower MI values at the distal esophagus with a progressive increase along the esophagus, with the former group having lower MI values at all levels than the latter group. The MI pattern in EoE was distinct from GERD in showing low MI values all along the esophagus.

patients with GERD. Important observations from our study include the following: (1) the MI pattern is unique in GERD compared with non-GERD patients; (2) low MI is an important determinant of changes along the esophageal epithelium, which is similar for GERD and those with EoE, but the MI pattern along the esophagus is distinctive in the 2 conditions; (3) GERD-related low MI recovers after PPI therapy; and (4) MI may be a better predictor of esophagitis than pH monitoring. These findings show that mucosal changes associated with chronic GERD may demonstrate a dose-response relationship along the esophageal axis, which is easily measurable using the MI device. In addition, we showed that EoE has a unique MI pattern, suggesting alteration in mucosal integrity all along the esophagus.

There are currently no techniques to accurately and reliably measure the mucosal consequence of long-term esophageal exposure to injurious gastroduodenal agents. As such, our data lay the foundation for in-depth investigation of direct measurements of MI as an alternative and innovative method for detecting GERD and its long-term impact on the esophageal mucosa with or without visible changes on endoscopy. The technique is simple and can be performed during endoscopy. It adds approximately 2 minutes to the procedure time and may ultimately eliminate the need for prolonged pH testing (ie, 24–48 hours). Existing diagnostic tests for GERD are inherently flawed because they rely on measurement of a single time point of intraluminal reflux (acid or nonacid) as a surrogate for a chronic condition. Current ambulatory reflux detection tests,

**Table 2.** MI Values ( $\Omega$ ) Along the Esophagus by Study Group

Location along the esophagus	E+ (n = 61)	E-/pH+ (n = 81)	E-/pH- (n = 93)	Achalasia (n = 18)	EoE (n = 15)	P value
Eroded mucosa	775 (613–1042)	—	—	—	—	—
Distance above the SCJ						
2 cm	1427 (880–2606)	1829 (1290–3020)	2956 (1858–4393)	5227 (3605–6948)	1235 (743–1353)	<.001
5 cm	2013 (1223–3440)	2455 (1611–3607)	4035 (2832–5648)	5227 (3604–6947)	1259 (978–1651)	<.001
10 cm	3236 (1743–4610)	3252 (2232–4990)	4806 (3438–6362)	5170 (4129–7768)	1365 (1112–1878)	<.001

NOTE. Values are median (IQR).

including pH monitoring (catheter or wireless) and multi-channel intraluminal impedance/pH monitoring, are limited in that they measure reflux events only over a 1- to 2-day period and assess acid exposure at a single location (5 cm above the LES), thus providing only a “snapshot” measurement of esophageal luminal acid exposure. More importantly, the catheter-based pH or impedance monitoring devices are invasive and uncomfortable and therefore may result in alteration of the patient’s daily activity, influencing the outcome they intend to measure. Thus, a simple accurate means of diagnosing chronic GERD is a welcome improvement to our current armamentarium of diagnostic testing. Our data expand on our original data<sup>25</sup> as well as recently published data (in a small sample size of 12 patients with GERD).<sup>29</sup> Unlike the MI catheter used by others,<sup>29</sup> our catheter underwent extensive validation to determine the size and separation of the MI rings to provide optimal sensitivity and specificity.<sup>25</sup> In addition, our current study included a large group of GERD and non-GERD patients to expand on the clinical utility.

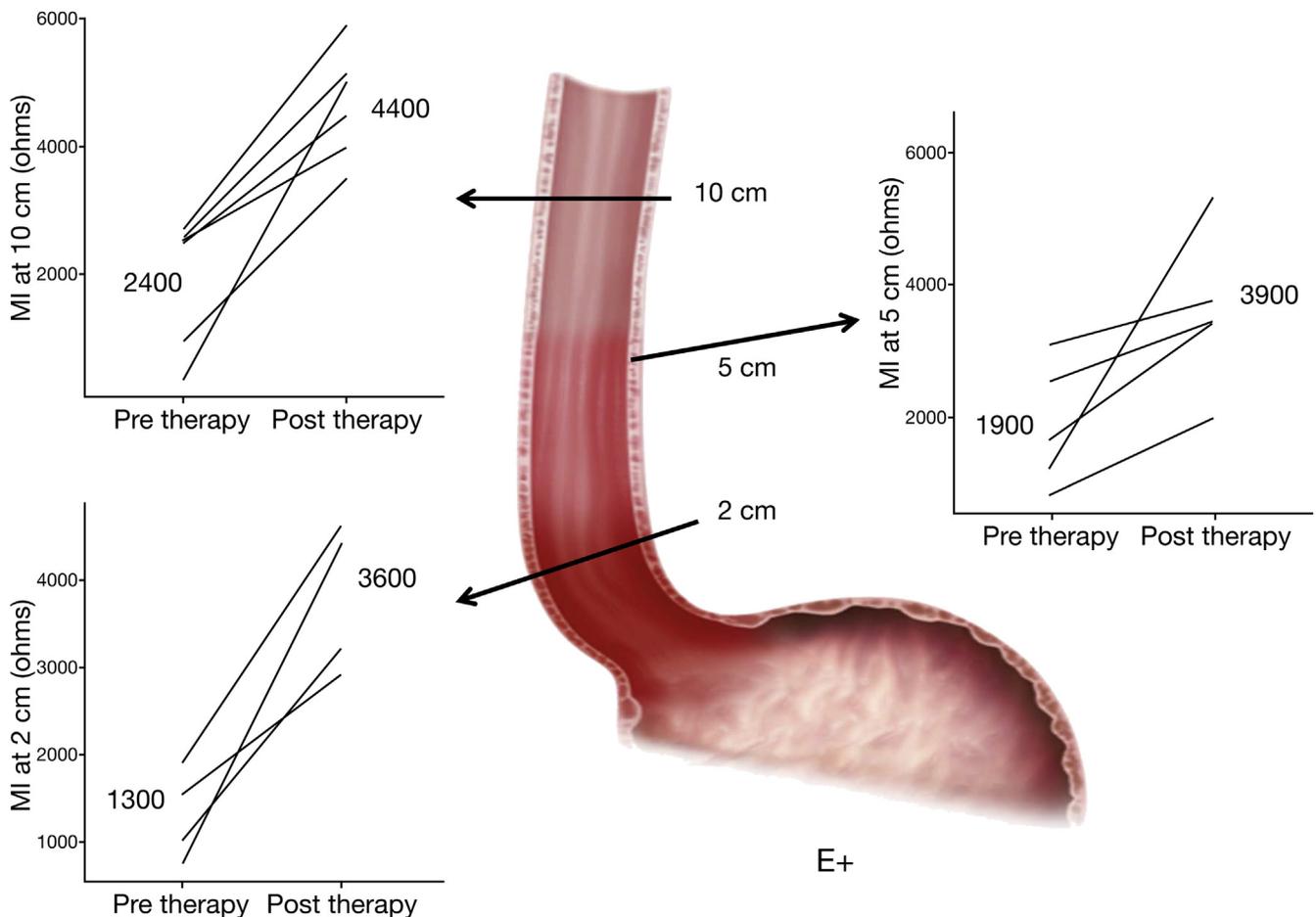
Investigations into reflux-induced alteration of esophageal mucosal integrity, such as by using this novel device, may offer a simple and convenient means to measure the severity and chronicity of reflux. Healthy esophageal epithelium has low permeability to intraluminal materials due to the integrity of cell membranes and tight junctions, which would correspond to high impedance values. However, injurious agents such as acid, pepsin, and/or bile acids compromise epithelial integrity. In fact, esophageal mucosal exposure to acid reflux is shown to decrease potential difference and epithelial resistance while increasing small molecule permeability,<sup>29</sup> which is consistent with DIS detected by transmission electron microscopy.<sup>18,30–35</sup> Distal esophageal biopsy specimens from patients with GERD are

reported to have significantly wider intercellular spaces compared with controls.<sup>16</sup> Subsequent studies have also suggested reversibility of DIS after acid suppressive therapy.<sup>33</sup> Several important constraints limit the use of this technique in diagnosis of GERD. DIS is sensitive but not specific for GERD and can occur under stress<sup>21</sup> in up to 30% of asymptomatic healthy subjects, in the setting of food allergy, and in other esophageal disorders such as candida infection.<sup>36</sup> Moreover, a recent study questioned the uniform presence of DIS in patients with GERD.<sup>23</sup> Furthermore, DIS is not homogeneously distributed in the esophagus of patients with GERD; instead, there appears to be radial and axial variation in its distribution.<sup>35</sup> Finally, the need for the expensive and not widely available expertise-dependent technology of electron microscopy has limited the use of DIS in GERD to only academic centers with special interest in esophageal diseases. A tool like the one used in this study that measures mucosal impedance as a surrogate marker for esophageal epithelial integrity can harness these differences and may improve accuracy in identifying patients with GERD from those without GERD.

Initial studies using intraluminal impedance monitoring suggested that patients with intestinal metaplasia (Barrett’s esophagus) or mucosal disruption (esophagitis) had lower intraluminal impedance values.<sup>37,38</sup> Thus, the prolonged ambulatory catheter was not as useful in measuring reflux in the group with known moderate to severe GERD. Therefore, the test was reserved for those with mainly nonerosive disease who continue to have symptoms despite lack of objective endoscopic evidence for GERD. Later studies suggested that baseline intraluminal impedance measurements may be inversely related to the degree of esophageal acid exposure.<sup>39</sup> For example, a study of 8 patients with erosive esophagitis, 18 patients with non-erosive reflux, and 15 healthy volunteers suggested lower intraluminal impedance in those with GERD than in healthy volunteers, indicating a potential role for this device in monitoring mucosal integrity.<sup>24</sup> Additionally, a recent study in infants with GERD suggested that intraluminal impedance increases after PPI therapy.<sup>40</sup> Taken together, these studies suggest that reflux-related changes are detectable via intraluminal impedance in patients with GERD. However, we believe that the preceding observations, performed crudely without confirmation of direct impedance sensor mucosal contact, were indirect measurements of mucosal integrity. The divergent impedance

**Table 3.** Test Characteristics of MI in GERD

Location above SCJ	2 cm	5 cm
Threshold ( $\Omega$ )	1465	2019
Sensitivity (%)	70	76
Specificity (%)	91	95
Predictive probability positive (%)	89	96
Predictive probability negative (%)	68	69
Likelihood ratio positive	6.98	12.1
Likelihood ratio negative	0.43	0.38

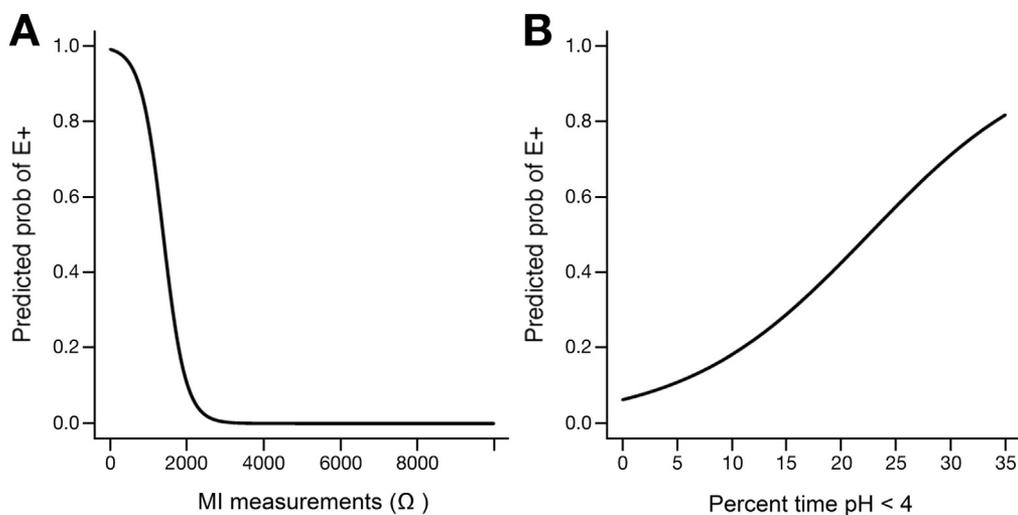


**Figure 3.** Median (IQR) MI values at 2, 5, and 10 cm above the SCJ in patients with esophagitis (E+) before and after PPI therapy. At all sites in the esophagus, the MI values increased significantly after PPI therapy.

values observed between intraluminal and mucosal impedance in patients with achalasia are a quintessential example of the limitation of the former technique over MI. An intraluminal impedance catheter submerged in a layer of food or liquid in achalasia results in artificially low impedance measurements,<sup>41,42</sup> which are overcome by direct mucosal measurement during endoscopy. Using our technique, any retained liquid can be suctioned at endoscopy, allowing for direct mucosal contact. As would be expected, MI values in patients with untreated achalasia should be similar to those without reflux (ie, control population), which is confirmed in our study (Figure 2). Our novel approach provided MI measurements via direct contact and short duration of measurements at endoscopy without the need for 24-hour, uncomfortable catheter-based devices and with reduced influence from unknown retained esophageal saliva or liquids.

We aimed to study the importance of MI in a setting that mimics current clinical evaluation of patients with suspected GERD. The role of abnormal esophageal acid exposure for the diagnosis of GERD is well established.<sup>43,44</sup> However, the role of intraluminal impedance testing alone without information on esophageal acid exposure is controversial in those who continue to be symptomatic despite PPI therapy. In fact, the

most recent American College of Gastroenterology and American Gastroenterological Association guidelines for the diagnosis and treatment of GERD minimize the role of intraluminal impedance monitoring due to lack of evidence-based outcome data.<sup>13,45</sup> In addition, the latest surgical outcome study showed that impedance monitoring does not predict response to fundoplication; however, baseline esophageal acid exposure as well as presence of a mechanical defect such as a hiatal hernia did predict symptomatic improvement after surgery.<sup>46</sup> Finally, the most recent Esophageal Diagnostic Advisory Panel, composed of medical and surgical experts on preoperative workup for GERD, emphasized the role of pH testing off therapy and suggested that there is insufficient evidence to justify the decision to proceed with antireflux surgery based on abnormal impedance testing alone.<sup>44</sup> Thus, our study assessed MI in those with objective evidence of reflux based on the currently used gold standard of diagnosis of GERD and those recommended by experts and guidelines. We propose that in patients being evaluated for chronic GERD, MI during endoscopy (on or off PPI therapy) will help guide the clinician to the presence of reflux. In those being tested before fundoplication or those who continue to be symptomatic despite acid suppressive therapy, measurements in the distal esophagus showing low



**Figure 4.** Predictive probability of esophagitis as a function of (A) MI or (B) percent time pH < 4. MI values less than 2000  $\Omega$  better predicted presence of GERD than pH monitoring.

MI (<2000  $\Omega$ ) would confirm the diagnosis of reflux and obviate the need for any further testing. Conversely, a high MI in these groups would argue against the presence of GERD and would suggest investigating alternative diagnoses.

An intriguing finding in our study is the pattern of esophageal MI in patients with EoE. In these patients, MI values were consistently low throughout the esophagus; this was distinct from the pattern observed in patients with GERD, showing a graded increase from the distal to proximal esophagus. Recent studies have confirmed the findings in our study showing impaired esophageal mucosal integrity in patients with EoE, which suggests that increased epithelial permeability has a possible role in the presentation of allergens to the immune system.<sup>47,48</sup> Currently under investigation is whether these changes are uniformly present at all sites along both the radial and axial distribution in EoE. A recent study by van Rhijn et al<sup>48</sup> suggests that PPI therapy may improve mucosal integrity in those with PPI-responsive EoE; however, this needs to be validated in the ongoing study with our device.

Some limitations and potential for design optimization of the MI device should be highlighted. First, the catheter used in our study contained only 2 impedance rings, forming a single MI sensing channel. It provided measurements along the esophagus at each of the sites: esophagitis and 2, 5, and 10 cm above the SCJ. The catheter was manually repositioned from one site to the next along the esophagus, which may have resulted in measurement variability. In addition, the 360° circumferential impedance ring design used in this study is not optimal. Because only 180° rings are needed to oppose the mucosa, the current design may have had interference from esophageal motility and intraluminal contents such as air and liquid. The next-generation device currently in development will have the ability to resolve these shortcomings, reduce measurement variability, and improve sensitivity to diagnose GERD. Finally, our measurements were taken only along the axial distribution of the esophagus. We believe that reflux changes along the esophageal mucosa do not occur uniformly, thus

necessitating both axial and radial MI measurements to provide more robust data. This will also be addressed in our future design updates to the MI catheter. The preceding adjustments in the catheter design, which are currently under way, will provide more robust MI data with reduced variability and decreased overlap among GERD and non-GERD subjects with potential for improved sensitivity. However, it is important to recognize that despite these limitations, the sensitivity and specificity of the current prototype device is similar to the available technology without the need for prolonged monitoring with uncomfortable catheter-based devices.

In conclusion, we have developed a novel, minimally invasive, short-duration MI technique for detecting esophageal mucosal changes due to chronic GERD without the need for 24- to 48-hour ambulatory impedance pH catheter placement. Our data show (1) an innovative method for differentiating the mucosal pattern in GERD compared with non-GERD, (2) recovery of GERD-related MI changes with PPI therapy, (3) distinction of the MI pattern from EoE, and (4) favorable detection of GERD compared with pH monitoring. Taken together, our findings are encouraging steps forward in improving our ability to diagnose GERD. Future improvements in device design will likely reduce measurement variability, thus improving device sensitivity for GERD and paving the way for a new means of reflux-related diagnoses.

## References

1. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900–1920; quiz 1943.
2. Spechler SJ, Jain SK, Tondler DA, et al. Racial differences in the frequency of symptoms and complications of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2002;16:1795–1800.
3. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology* 2002;122:1500–1511.

4. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol* 2006;101:2128–2138.
5. Ofman JJ. The economic and quality-of-life impact of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 2003;98:S8–S14.
6. Fenter TC, Naslund MJ, Shah MB, et al. The cost of treating the 10 most prevalent diseases in men 50 years of age or older. *Am J Manag Care* 2006;12:S90–S98.
7. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology* 2009;136:376–386.
8. Fass R, Gasiorowska A. Refractory GERD: what is it? *Curr Gastroenterol Rep* 2008;10:252–257.
9. Richter JE. How to manage refractory GERD. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:658–664.
10. Lacy BE, Weiser K, Chertoff J, et al. The diagnosis of gastroesophageal reflux disease. *Am J Med* 2010;123:583–592.
11. Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. *Gastroenterology* 1996;110:1982–1996.
12. Dent J. Gastro-oesophageal reflux disease. *Digestion* 1998;59:433–445.
13. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1392–1413. 1413 e1–5.
14. Vaezi MF, Schroeder PL, Richter JE. Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring. *Am J Gastroenterol* 1997;92:825–829.
15. Vaezi MF. Role of impedance/pH monitoring in refractory GERD: let's be careful out there! *Gastroenterology* 2007;132:1621–1622; discussion 1622.
16. Tobey NA, Carson JL, Alkief RA, et al. Dilated intercellular spaces: a morphological feature of acid reflux—damaged human esophageal epithelium. *Gastroenterology* 1996;111:1200–1205.
17. Caviglia R, Ribolsi M, Gentile M, et al. Dilated intercellular spaces and acid reflux at the distal and proximal oesophagus in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007;25:629–636.
18. Caviglia R, Ribolsi M, Maggiano N, et al. Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. *Am J Gastroenterol* 2005;100:543–548.
19. Orlando RC, Bryson JC, Powell DW. Mechanisms of H<sup>+</sup> injury in rabbit esophageal epithelium. *Am J Physiol* 1984;246:G718–G724.
20. Tobey NA, Hosseini SS, Caymaz-Bor C, et al. The role of pepsin in acid injury to esophageal epithelium. *Am J Gastroenterol* 2001;96:3062–3070.
21. Farre R, De Vos R, Geboes K, et al. Critical role of stress in increased oesophageal mucosa permeability and dilated intercellular spaces. *Gut* 2007;56:1191–1197.
22. Ribolsi M, Perrone G, Caviglia R, et al. Intercellular space diameters of the oesophageal epithelium in NERD patients: head to head comparison between light and electron microscopy analysis. *Dig Liver Dis* 2009;41:9–14.
23. Vaezi MF, Slaughter JC, Smith BS, et al. Dilated intercellular space in chronic laryngitis and gastro-oesophageal reflux disease: at baseline and post-lansoprazole therapy. *Aliment Pharmacol Ther* 2010;32:916–924.
24. Farre R, Blondeau K, Clement D, et al. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. *Gut* 2011;60:885–892.
25. Saritas Yuksel E, Higginbotham T, Slaughter JC, et al. Use of direct, endoscopic-guided measurements of mucosal impedance in diagnosis of gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2012;10:1110–1116.
26. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013;108:679–692.
27. Pritchett JM, Aslam M, Slaughter JC, et al. Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. *Clin Gastroenterol Hepatol* 2009;7:743–748.
28. Pandolfino JE, Richter JE, Ours T, et al. Ambulatory esophageal pH monitoring using a wireless system. *Am J Gastroenterol* 2003;98:740–749.
29. Tobey NA, Hosseini SS, Argote CM, et al. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. *Am J Gastroenterol* 2004;99:13–22.
30. Carney CN, Orlando RC, Powell DW, et al. Morphologic alterations in early acid-induced epithelial injury of the rabbit esophagus. *Lab Invest* 1981;45:198–208.
31. Orlando RC, Powell DW, Carney CN. Pathophysiology of acute acid injury in rabbit esophageal epithelium. *J Clin Invest* 1981;68:286–293.
32. Farre R, Fornari F, Blondeau K, et al. Acid and weakly acidic solutions impair mucosal integrity of distal exposed and proximal non-exposed human oesophagus. *Gut* 2010;59:164–169.
33. Calabrese C, Bortolotti M, Fabbri A, et al. Reversibility of GERD ultrastructural alterations and relief of symptoms after omeprazole treatment. *Am J Gastroenterol* 2005;100:537–542.
34. Calabrese C, Fabbri A, Bortolotti M, et al. Dilated intercellular spaces as a marker of oesophageal damage: comparative results in gastro-oesophageal reflux disease with or without bile reflux. *Aliment Pharmacol Ther* 2003;18:525–532.
35. Edebo A, Vieth M, Tam W, et al. Circumferential and axial distribution of esophageal mucosal damage in reflux disease. *Dis Esophagus* 2007;20:232–238.
36. van Malenstein H, Farre R, Sifrim D. Esophageal dilated intercellular spaces (DIS) and nonerosive reflux disease. *Am J Gastroenterol* 2008;103:1021–1028.
37. Al-Zaben A, Chandrasekar V. Effect of esophagus status and catheter configuration on multiple intraluminal impedance measurements. *Physiol Meas* 2005;26:229–238.

38. Vela MF. Multichannel intraluminal impedance and pH monitoring in gastroesophageal reflux disease. *Expert Rev Gastroenterol Hepatol* 2008;2:665–672.
39. Kessing BF, Bredenoord AJ, Weijnen PW, et al. Esophageal acid exposure decreases intraluminal baseline impedance levels. *Am J Gastroenterol* 2011;106:2093–2097.
40. Loots CM, Van Wijk MP, Smits MJ, et al. Measurement of mucosal conductivity by MII is a potential marker of mucosal integrity restored in infants on acid-suppression therapy. *J Pediatr Gastroenterol Nutr* 2011;53:120–123.
41. Nguyen HN, Domingues GR, Winograd R, et al. Impedance characteristics of esophageal motor function in achalasia. *Dis Esophagus* 2004;17:44–50.
42. Heard R, Castell J, Castell DO, et al. Characterization of patients with low baseline impedance on multichannel intraluminal impedance-pH reflux testing. *J Clin Gastroenterol* 2012;46:e55–e57.
43. Vaezi MF, Richter JE. Role of acid and duodenogastroesophageal reflux in gastroesophageal reflux disease. *Gastroenterology* 1996;111:1192–1199.
44. Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. *J Am Coll Surg* 2013;217:586–597.
45. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–328; quiz 329.
46. Francis DO, Goutte M, Slaughter JC, et al. Traditional reflux parameters and not impedance monitoring predict outcome after fundoplication in extraesophageal reflux. *Laryngoscope* 2011;121:1902–1909.
47. Mueller S, Neureiter D, Aigner T, et al. Comparison of histological parameters for the diagnosis of eosinophilic oesophagitis versus gastro-oesophageal reflux disease on oesophageal biopsy material. *Histopathology* 2008;53:676–684.
48. van Rhijn BD, Weijnen PW, Verheij J, et al. Proton pump inhibitors partially restore mucosal integrity in patients with proton pump inhibitor-responsive esophageal eosinophilia but not eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2014;12:1815–1823.e2.

---

Received June 12, 2014. Accepted October 14, 2014.

#### Reprint requests

Address requests for reprints to: Michael F. Vaezi, MD, PhD, MSc (Epi), Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, 1660 TVC, 1301 22nd Avenue South, Nashville, Tennessee 37232-5280. e-mail: michael.vaezi@vanderbilt.edu; fax: (615) 322-8525.

#### Acknowledgments

Partial support for Dr. Ates's salary was made possible by a kind financial contribution from The Bill and Carol Latimer Charitable Trust.

#### Conflicts of interest

The authors disclose the following: J.M. is affiliated with Sandhill Scientific Inc (Denver, CO), which helped design the special mucosal impedance catheter used in this study. His involvement in the study was provision of technical support for the catheter design. He had no influence on the study design, conduct, analysis, or final manuscript. Vanderbilt University and Sandhill Scientific Inc jointly hold a patent on the mucosal impedance concept and device. Otherwise, there are no financial relationships between any of the other authors and Sandhill Scientific Inc. This was disclosed to the patients who participated in this study. The remaining authors disclose no conflicts.