Esophageal Mucosal Impedance Pattern is Distinct in Patients With Extraesophageal Reflux Symptoms and Pathologic Acid Reflux


Summary: Objectives/study design. Current diagnostic tests for gastroesophageal reflux disease (GERD) do not consistently measure chronicity of reflux. Mucosal impedance (MI) is a minimally invasive measurement to assess esophageal conductivity changes due to GERD. We aimed to investigate MI pattern in patients with symptoms of extraesophageal reflux (EER) in a prospective longitudinal cohort study.

Methods. Patients with potential symptoms of EER undergoing esophagogastroduodenoscopy (EGD) with wireless pH monitoring were studied. Participants included those with erosive esophagitis (E+), normal EGD/abnormal pH (E+/pH+), and normal EGD/normal pH (E−/pH−). MI was measured from the site of injury in patients with E+, as well as at 2, 5, and 10 cm above the squamocolumnar junction (SCJ) in all participants.

Results. Forty-one patients with symptoms of EER were studied. MI measurements at 2 cm above the SCJ were significantly (P = 0.04) different among the three groups, with MI lowest for E+ and greatest for E−/pH− patients. Although not statistically significant, there is a graded increase in median (interquartile range) MI axially along the esophagus at 5 cm (P = 0.20) and at 10 cm (P = 0.27) above the SCJ, with those with reflux (E+ and E−/pH+) having a lower MI than those without.

Conclusions. Patients with symptoms of EER and evidence of acid reflux have an MI lower than those without at 2 cm above the SCJ, with a trend at 5 cm and 10 cm as well. MI may be a tool to assess presence of GERD in patients presenting with EER symptoms.

Key Words: mucosal impedance–GERD–reflux–extraesophageal reflux–diagnosis.

INTRODUCTION

Extraesophageal reflux (EER) is widely implicated in the etiology of laryngeal, pharyngeal, and pulmonary symptoms, and controversy exists regarding the diagnosis and management of this condition.1 Patients with presumed EER refractory to initial empiric medical therapy are often referred for further testing. Current guidelines recommend diagnostic testing, which can include the use of upper endoscopy and pH and/or impedance monitoring.2 Available diagnostic tests for gastroesophageal reflux disease (GERD) are suboptimal and lack adequate sensitivity and specificity and only detect reflux events during the 24–96 hour testing period. This can lead to false-negative results for patients, leading to alternative diagnoses and may alter treatment regimens.3,4 Evaluation and treatment of suspected EER symptoms is shown to contribute substantially to health-care expenditures.5 This economic burden is greater for those with EER than for those with GERD, a factor that is predominantly driven by excessive use of proton pump inhibitors. Thus, there is an urgent need for improved means of diagnosing reflux-related extraesophageal symptoms.

Current diagnostic modalities to evaluate patients with GERD and those with EER include several tests of varying utility. Esophageal erosions observed at the time of esophagogastroduodenoscopy (EGD) are highly specific for GERD; however, these findings lack sensitivity as less than 30% of patients with GERD exhibit erosive disease. Many patients exhibit normal-appearing esophageal mucosa at the time of endoscopy in the setting of widespread use of acid-suppressive medications. Ambulatory pH testing and intraluminal impedance monitoring are the current gold standard but are limited as these tests can only measure reflux events during a limited testing window, which can be impacted by patient compliance with routine activity in the setting of an intranasal catheter.5–7

The presence of dilated intercellular spaces (DIS) as observed on transmission electron microscopy of biopsy specimens is suggested as a marker of chronicity of GERD in patients with either esophagitis or non-erosive reflux disease.5–10 In animal models, DIS is a consequence of acid-peptic injury to the apical surface of epithelial cells and of acute stress, increasing paracellular permeability across epithelial layers and likely allowing diffusion of H+ ions into the intercellular space.11–13 H+ access to sensory nerve endings in the mucosa may account for symptoms that occur in those without mucosal breaks.14 Despite these findings, the role of DIS in diagnosing GERD remains unknown owing to uncertainty regarding site of optimal biopsy, need for costly and not widely available transmission electron microscopy, and recent contradictory findings.15
Measuring esophageal intraluminal impedance has suggested lower intraluminal impedance values for those with GERD compared with controls.\textsuperscript{16} This finding is based on traditional catheter-based 24-hour ambulatory impedance measurements. This technology uses indirect measurement of mucosal conductivity at a fixed site along the esophagus and is hampered by patient discomfort. The measurements of intraluminal impedance are indirect and there is uncertainty regarding direct contact with mucosa. These measurements are associated with suboptimal sensor array and impedance rings that are too far apart (typically 1.6 cm). There is less certainty regarding whether the measurements are impacted by intraluminal contents, which by design cannot be excluded, yielding inherent errors in measurement.

We developed and validated a minimally invasive, simple, low-cost device to assess changes in esophageal mucosal impedance (MI) as a tool to measure the presence and chronicity of reflux.\textsuperscript{17} A recent study showed that measurements of MI detect GERD with a higher level of specificity and positive predictive value than wireless pH monitoring.\textsuperscript{18} The aim of this prospective longitudinal study was to investigate MI pattern in patients with symptoms of EER.

**MATERIALS AND METHODS**

The 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.

**Study design and patient population**

The study population consisted of patients with suspected reflux-associated extraesophageal symptoms referred to the Esophageal Motility Center at Vanderbilt University Medical Center for evaluation and treatment. The following data were collected for all patients: presence, severity, and frequency of GERD symptoms (heartburn \pm regurgitation) and extraesophageal symptoms (cough, hoarseness, asthma, postnasal drip, rhinitis, or seasonal allergies and sinusitis); current medications; and demographic data (age, sex, race, body mass index). All patients were referred for evaluation of the potential role of GERD as an etiology of their symptoms.

Patients underwent EGD and wireless 48-hour pH monitoring (off acid-suppressive therapy) as part of their routine care. Reflux testing was performed to confirm esophageal acid exposure in those with an incomplete response to acid-suppressive medications as part of an evaluation to assess for GERD as the etiology of symptoms. MI was assessed at the time of endoscopy 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. We assessed MI at the site of eroded mucosa if present, as well as at 2, 5, and 10 cm above the squamocolumnar junction (SCJ) relative to the lesser curvature of the stomach. MI measurements were obtained 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 classified as having erosive esophagitis, non-erosive GERD (no evidence of esophagitis on endoscopy with abnormal pH testing), or not having GERD (no esophagitis on endoscopy and unremarkable pH testing results). MI values for groups were compared with each other and at different levels along the esophageal axis.

Inclusion criteria were age greater than 18 years and chronic EER symptoms. Patients were excluded from the study if they were unwilling to undergo testing, were pregnant, if they had Barrett esophagus, had a history of esophageal surgery or gastrointestinal cancer, had peptic ulcer disease, did not discontinue the use of proton pump inhibitors 10 days before endoscopy and histamine receptor antagonists 7 days before endoscopy, or if they had a serious illness that would interfere with study participation.

**Measurement of MI**

The MI catheter was designed to assess electrical impedance of the esophageal lining via direct mucosal contact. Details have been described previously,\textsuperscript{19} but in brief, a special sensor array composed of 360-degree circumferential sensing rings (Sandhill Scientific Inc, Highlands Ranch, Colorado, USA) was engineered and mounted on a catheter 2 mm in diameter 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 \textmu 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, Highlands Ranch, Colorado, USA) and were viewed and analyzed by using BioView analysis software (Sandhill Scientific Inc).

**Wireless pH monitoring**

Ambulatory pH monitoring was performed for 48 hours using Bravo wireless pH monitors (Given Imaging, Duluth, GA, USA). 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 were then placed as previously described.\textsuperscript{19} 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.\textsuperscript{20}
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