Clinical Gastroenterology and Hepatology 2015;13:1242–1248

ALIMENTARY TRACT

Endoscopic Mucosal Impedance Measurements Correlate With Eosinophilia and Dilation of Intercellular Spaces in Patients With Eosinophilic Esophagitis

David A. Katzka,[*] Karthik Ravi,[*] Debra M. Geno,[*] Thomas C. Smyrk,[‡] Prasad G. Iyer,[*] Jeffrey A. Alexander,[*] Jerry E. Mabary,[§] Michael Camilleri,[*] and Michael F. Vaezi[‖]

*Division of Gastroenterology and Hepatology, ‡Department of Pathology, Mayo Clinic, Rochester, Minnesota; §Sandhill Scientific, Inc, Highlands Ranch, Colorado; ‖Division of Gastroenterology and Hepatology, Vanderbilt University, Nashville, Tennessee

BACKGROUND & AIMS: **Penetration of the esophageal epithelium by food antigens is an early event in the pathogenesis of eosinophilic esophagitis (EoE), but the precise relationship among eosinophilia, dilated intercellular spaces (DIS), and decreased barrier function is unclear. We investigated the correlation between site-specific mucosal impedance (MI) measurements of ion flux and esophageal histology, and whether MI measurements can be used to distinguish between patients with active and inactive EoE.**

METHODS: **MI was measured (in Ω) in 10 patients with active EoE (>15 eosinophils [eos]/high-power field [HPF]) and in 10 with inactive EoE (<15 eos/HPF, as a result of treatment), and mucosal biopsy specimens were collected from 4 esophageal sites (2, 5, 10, and 15 cm above the Z-line). MI also was measured in 10 individuals without esophageal symptoms (controls). MI measurements, eos/HPF, and DIS grade were compared among patients with EoE and controls.**

RESULTS: **The esophageal MI values were significantly lower in patients with active EoE (1909 Ω) compared with inactive EoE (4349 Ω) or controls (5530 Ω) ($P < .001$). Biopsy specimens from 4 patients with active EoE contained fewer than 15 eos/HPF and lower-grade DIS than in patients with active disease. There were significant inverse correlations between MI and eos/HPF (rs = -.584), as well as between MI and DIS (rs = -.531; $P < .001$). The MI cut-off value of 2300 Ω identified patients with active EoE with 90% sensitivity and 91% specificity, and high-grade DIS with 89% sensitivity and 82% specificity.**

CONCLUSIONS: **In patients with EoE, eosinophilia and DIS correlate with MI measurements of ion flux. Endoscopic MI measurement in the esophagus is safe and easy to perform, and can be used to assess activity of diseases such as EoE.**

Keywords: Allergy; Epithelial Permeability; Spongiosis; Transepithelial Resistance; Diagnostic; Diagnosis.

One of the mechanisms of eosinophilic esophagitis is exposure of food antigens to antigen recognition cells in the esophageal mucosa, which initiates a chronic allergy-based inflammatory response.[1,2] It is believed that this exposure is facilitated through dilation of the intercellular spaces (DIS) between esophageal epithelial cells (termed *spongiosis*). This has been substantiated by several studies that have shown the following: first, DIS is found commonly in biopsy specimens from patients with active EoE and reverses with steroid therapy[3]; and, second, DIS correlates to a physiologic demonstration of increased esophageal epithelial permeability as shown through transepithelial small-molecule flux in mucosal biopsy specimens appraised in Ussing chambers.[4]

Recently, a new endoscopically placed probe has been developed that may measure epithelial impedance over a 2-cm area.[5] By measuring current generated by ion flow, this device provides a measure of transepithelial resistance and permeability because there are no ion transporters in the esophageal epithelium. By using a through-the-scope MI measurement device we recently showed the clinical utility of MI measurement in differentiating

Abbreviations used in this paper: DIS, dilated intercellular spaces; eos/HPF, eosinophils per high-power field; GERD, gastroesophageal reflux disease; MI, mucosal impedance; PPI, proton pump inhibitor.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.12.032

gastroesophageal reflux disease (GERD) from non-GERD.[6] These in-depth studies have shown the feasibility of the MI measuring device and shown lower epithelial impedance in patients with GERD than in controls. This also was shown in patients with eosinophilic esophagitis but only with stationary blindly positioned transnasal intraluminal combined pH/impedance probes.[4,7]

Although this information provides insight into the mechanism of EoE, the precise relationship between these in vivo measurements and histologic findings of esophageal epithelial eosinophilia and DIS is not clear, particularly because EoE is known to be a patchy disease, especially with reference to eosinophil distribution.[8,9] Furthermore, if a close correlation could be shown between these parameters, performance of esophageal MI measurement with an endoscopically passed, easy-to-use impedance probe may serve as an excellent marker for active EoE. This would be particularly valuable for more comprehensively assessing mucosal inflammation at diagnosis and when assessing therapy response, once the diagnosis has been established. Furthermore, this could obviate the need to perform repeat biopsies.

Our hypothesis was that reduced impedance would reflect EoE activity as measured by objective markers of eosinophil infiltration and DIS. Our aim was to obtain impedance measurements in active and inactive EoE patients at the location of endoscopic biopsies to better characterize the relationship between impedance and histologic hallmarks of EoE.

Methods

Study Patients

Patients with eosinophilic esophagitis and control patients participated in this study. The presence of EoE was defined by consensus guidelines, that is, more than 15 eosinophils per high-power field (eos/HPF) on esophageal biopsy, esophageal symptoms, and lack of a histologic response to a 2-month course of a proton pump inhibitor. Patients with active EoE maintained more than 15 eos/HPF, whereas patients who were inactive as a result of treatment had fewer than 15 eos/HPF. Control patients were those undergoing clinically indicated upper endoscopy for nonesophageal symptoms in whom a normal-appearing esophagus was found at the time of endoscopy. Control patients were excluded if they had any history of esophageal symptoms; regular use of proton pump inhibitors, H2 antagonists, or antacids; smoking; use of medications reported to cause esophageal injury such as bisphosphonates or nonsteroidal anti-inflammatory drugs; alcoholism; or prior upper gastrointestinal surgery.

Esophageal Impedance Measurement

A previously described mucosal impedance (MI) catheter 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, Highlands Ranch, CO) was engineered and mounted on a 2-mm–diameter catheter with the following specifications: (1) ring length of 2 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 2.5 μA root mean square 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, according to Ohm's law (voltage = current/resistance). Data were acquired with a stationary impedance data acquisition system (InSight; Sandhill Scientific, Inc) and were viewed and analyzed on BioView Analysis software (Sandhill Scientific, Inc). Impedance measurements were obtained at 2, 5, 10, and 15 cm above the gastroesophageal junction. In instances in which a stable baseline measurement could not be obtained (most commonly owing to excess fluid present), the data were not included. Similarly, in 2 patients, 3 sets of esophageal biopsy specimens were taken at 2 or 5 and 10 or 15 cm above the gastroesophageal junction, and these were the same locations where the impedance probe measurements were recorded. In 1 patient, biopsy specimens were taken at only one level.

Histologic Analysis

Biopsy specimens were stained with H&E and first read by a single experienced gastrointestinal pathologist (T.C.S.) using a Nikon E600 microscope (Nikon Instruments Inc, Melville, NY) with a 10 × 25 ultra wide eyepiece. These biopsy specimens also were obtained at 2, 5, 10, and 15 cm above the gastroesophageal junction in the same location (typically the left lateral esophageal wall) where the impedance measurement was made.

Eosinophil counts. The area of greatest eosinophil density first was located by low-powered review of all tissue submitted from a given location. The area of greatest eosinophil density on esophageal biopsy specimen was used for analysis in each individual patient regardless of esophageal location. Eosinophils then were counted using a 40× objective, a field diameter of 0.625 mm, and a field area of 0.307 mm^2. The peak eos/HPF was reported. From the area of greatest eosinophil density under low-powered review, 5 random fields were chosen. Peak eosinophil counts from these 5 fields then were used to calculate a mean eosinophil count.

Dilated intercellular spaces (spongiosis). Dilated intercellular spaces (spongiosis) was graded on the basis of the worst area, using a scale of 0 to 4+ as previously described.[3] Briefly, DIS grading was assessed by the appearance of the tight junctions seen on biopsy and the