Esophageal Intraluminal Baseline Impedance Differentiates Gastroesophageal Reflux Disease From Functional Heartburn

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BACKGROUND & AIMS: Mucosal integrity can be assessed in patients with gastroesophageal reflux disease (GERD) by measuring intraluminal baseline impedance (BI). However, it is not clear whether BI is abnormal in patients with functional heartburn (FH), or can be used to distinguish them from patients with GERD. We compared differences in BI between patients with FH vs GERD.

METHODS: We performed a prospective study of 52 patients (16 men; mean age, 55 y; range, 23–78 y) seen at a tertiary university hospital from February 2009 through December 2012. Thirty-five patients had GERD (19 had nonerosive reflux disease [NERD], 16 had erosive reflux disease [ERD]) and 17 had FH. All patients discontinued proton pump inhibitor therapy and then underwent esophagogastroduodenoscopy and multichannel intraluminal impedance and pH monitoring. BI was assessed at 3, 5, 7, 9, 15, and 17 cm proximal to the lower esophageal sphincter in recumbent patients. Biopsy specimens were taken from 3 cm above the gastroesophageal junction; histology analysis was performed to identify and semiquantitatively score (scale, 0–3) dilated intercellular spaces.

RESULTS: Baseline impedance in the distal esophagus was significantly lower in patients with NERD or erosive reflux disease (ERD) than FH ($P = .0006$). At a cut-off value of less than 2100 Ω, BI measurements identified patients with GERD with 78% sensitivity and 71% specificity, with positive and negative predictive values of 75%. Also in the proximal esophagus, reduced levels of BI levels were found only in patients with ERD. There were negative correlations between level of BI and acid exposure time ($r = -0.45$; $P = .0008$), number of acidic reflux episodes ($r = -0.45$; $P = .001$), and proximal extent ($r = -0.40$; $P = .004$). Biopsy specimens from patients with NERD or ERD had significant increases in dilation of intercellular spaces, compared with those from patients with FH; there was an inverse association between dilated intercellular spaces and BI in the distal esophagus ($r = -0.28$; $P = .06$).

CONCLUSIONS: Measurement of BI in the lower esophagus can differentiate patients with ERD or NERD from patients with FH (78% sensitivity and 71% specificity), and therefore should be considered as a diagnostic tool for patients with proton pump inhibitor–refractory reflux. Low levels of BI are associated with increased exposure to acid and dilation of intercellular spaces, indicating that BI is a marker of mucosal integrity.

Keywords: MII-pH; Esophageal Mucosa; Acid-Suppressive Therapy; Diagnosis.

The esophageal squamous epithelium is a tight protective barrier against luminal components. Disruption of this epithelial defense is a common phenomenon in gastroesophageal reflux disease (GERD), even in the absence of lesions visible at endoscopy (nonerosive reflux disease [NERD]). Microscopic alterations and dilation of cell–cell contacts usually are found in GERD and are associated with impaired mucosal integrity.[1–3] In addition, in NERD, altered microscopic architecture with dilated intercellular spaces has been

linked to impaired transepithelial permeability in several functional studies.[4] Besides the measurements of transepithelial electrical resistance and permeability in Ussing chambers, impaired mucosal integrity has been associated with in vivo assessment of esophageal baseline impedance (BI).[5,6] In a rabbit model, perfusion with acidified solution was found to reduce BI levels, which persisted even beyond the end of perfusion. Ex vivo, BI levels correlated with transepithelial electrical resistance in Ussing chambers and with dilated intercellular spaces.[5] Patients with GERD have lower BI impedance levels compared with asymptomatic controls as well as with symptomatic patients with normal acid exposure of the distal esophagus. Furthermore, these changes have normalized with increasing BI levels after acid-suppressive therapy.[6]

In clinical practice, NERD is the most frequently diagnosed entity of GERD but poses a diagnostic challenge to conditions that are not GERD related (ie, functional heartburn [FH]).[7] In case of a normal pH-impedance analysis without symptom association, the diagnosis most likely is FH with no or only a weak response to acid-suppressive therapy.[8] Several studies have addressed the assessment of morphologic changes in esophageal mucosa and were able to distinguish NERD from FH by using transmission electron microscopy as well as standard histopathologic evaluation.[9–11]

To date, functional investigations to assess intramucosal BI levels showing impaired mucosal integrity with respect to histomorphologic alterations have not been performed to differentiate FH from GERD. The aim of our study was to assess BI levels in patients with FH and to differentiate them from GERD. We further aimed to evaluate histomorphologic alterations such as dilated intercellular spaces (DIS) to correlate with BI levels as a parameter of mucosal electrical conductivity and integrity.

Methods

Study Subjects and Study Protocol

Fifty-two consecutive patients (16 men, 36 women; age, 55 y; [23–78]) were referred to our outpatient department and functional gastrointestinal laboratory and investigated for typical reflux symptoms (heartburn and acid regurgitation). In this prospective study we enrolled 17 patients with FH (age, 53.8 y; [23–78 y]). By definition, these patients suffered from proton pump inhibitor (PPI)-refractory heartburn with less than 50% symptom improvement and a past medical history of a PPI double standard dose for at least 6 weeks. Diagnostic criteria for FH were a normal endoscopic appearance of the gastroesophageal junction in combination with normal acid exposure time without any symptom association (negative symptom index [SI] and symptom association probability [SAP]) (see later). In addition, 16 patients with erosive reflux disease (ERD) (age, 53.8 y;

[23–78 y]) and 19 patients with NERD (age, 64.9 y; [56–72 y]), including patients with esophageal hypersensitivity, were investigated.

All patients were interviewed and clinically characterized before planning further diagnostic steps. The patients were asked to taper and stop potential acid-suppressive medication for at least 3 weeks before endoscopy and impedance pH monitoring (MII-pH) to minimize effects of potential acid hypersecretion on BI levels and histology. Symptoms were recorded using the validated reflux disease questionnaire translated into German,[19] and all patients were scheduled to be investigated endoscopically and by MII-pH monitoring on the same day.

The study protocol was performed according to the Declaration of Helsinki and approved by the local ethical committee. Eligible patients (>18 y) were included after providing informed consent. None of the patients had an esophagogastroduodenoscopy or functional diagnostics previously, but all patients had heartburn as a typical GERD symptom based on the Montreal classification.[12] Previous upper gastrointestinal surgery, alarm symptoms, gastric or duodenal ulcer disease, Barrett's esophagus, or esophageal motility disorders were considered exclusion criteria.

Upper Gastrointestinal Endoscopy and Esophageal Biopsy Specimens

After an overnight fast, all patients underwent an esophagogastroduodenoscopy under intravenous conscious sedation using midazolam (Dormicum V 5 mg/mL; Roche Deutschland Holding GmbH, Penzberg, Germany) and/or 1% propofol (Propofol-Lipuro 10 mg/mL; Braun Melsungen AG, Melsungen, Germany) with a standard videogastroscope (GIFQ180; Olympus Optical Europe, Hamburg, Germany).

Endoscopic esophageal landmarks were defined as the gastroesophageal junction, with the beginning of the gastric folds and the Z-line as the squamocolumnar junction and diaphragmatic pinch. In the distal esophagus, 2 esophageal biopsy specimens were taken from 3 to 5 cm above the gastroesophageal junction, not including visible changes (no erosions), and immediately transferred to 4% neutral-buffered formalin for later embedding in paraffin.

Combined 24-Hour Impedance pH Monitoring and Assessment of Intraluminal Baseline Impedance Levels

After endoscopy, the MII-pH catheter (Sandhill Scientific, Highland Ranch, CO) was inserted and located with esophageal pH electrodes 5 cm above the gastroesophageal junction (lower esophageal sphincter [LES]). Manometry was not performed in all patients to localize the LES. In a subset of patients, localization of the LES and placement of the MII-pH catheter was performed