Association Between Baseline Impedance Values and Response Proton Pump Inhibitors in Patients With Heartburn

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BACKGROUND & AIMS: Esophageal impedance measurements have been proposed to indicate the status of the esophageal mucosa, and might be used to study the roles of the impaired mucosal integrity and increased acid sensitivity in patients with heartburn. We compared baseline impedance levels among patients with heartburn who did and did not respond to proton pump inhibitor (PPI) therapy, along with the pathophysiological characteristics of functional heartburn (FH).

METHODS: In a case-control study, we collected data from January to December 2013 on patients with heartburn and normal findings from endoscopy who were not receiving PPI therapy and underwent impedance pH testing at hospitals in Italy. Patients with negative test results were placed on an 8-week course of PPI therapy (84 patients received esomeprazole and 36 patients received pantoprazole). Patients with more than 50% symptom improvement were classified as FH/PPI responders and patients with less than 50% symptom improvement were classified as FH/PPI nonresponders. Patients with hypersensitive esophagus and healthy volunteers served as controls. In all patients and controls, we measured acid exposure time, number of reflux events, baseline impedance, and swallow-induced peristaltic wave indices.

RESULTS: FH/PPI responders had higher acid exposure times, numbers of reflux events, and acid refluxes compared with FH/PPI nonresponders ($P < .05$). Patients with hypersensitive esophagus had mean acid exposure times and numbers of reflux events similar to those of FH/PPI responders. Baseline impedance levels were lower in FH/PPI responders and patients with hypersensitive esophagus, compared with FH/PPI nonresponders and healthy volunteers ($P < .001$). Swallow-induced peristaltic wave indices were similar between FH/PPI responders and patients with hypersensitive esophagus.

CONCLUSIONS: Patients with FH who respond to PPI therapy have impedance pH features similar to those of patients with hypersensitive esophagus. Baseline impedance measurements might allow for identification of patients who respond to PPIs but would be classified as having FH based on conventional impedance-pH measurements.

Keywords: GERD; pH Monitoring; Functional GI Disorder; pH-Impedance Monitoring.

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Nonerosive reflux disease (NERD) patients are markedly heterogeneous from both a pathophysiological and clinical point of view, and should be characterized appropriately by means of 24-hour esophageal multichannel intraluminal impedance and pH monitoring (MII-pH).[1] Indeed, the advent of MII-pH has enabled the identification of acid, weakly acidic, and weakly alkaline refluxes with a consequent added value

in differentiating patients with hypersensitive esophagus (HE) (ie, negative endoscopy, physiological acid exposure time, AET, and positive symptom-reflux association) from patients with functional heartburn (FH) (ie, negative endoscopy, physiological AET, negative symptom-reflux association, and a negative response to acid suppression therapy).[2–4] On the other hand, recent studies highlighted some MII-pH limitations, such as the day-to-day variability or the drawbacks of the current reflux-symptom association indexes.[5,6] In addition, the response to proton pump inhibitors (PPIs) has limited the ability to identify gastroesophageal reflux disease (GERD) patients.[7–9]

Recently, it was suggested that low esophageal basal impedance measurements may reflect the status of the esophageal mucosa and thus may be used to study the role of the impaired mucosal integrity and increased acid sensitivity in patients with heartburn.[10–12] According to previous findings, baseline impedance levels may be useful to increase the diagnostic sensitivity of MII-pH monitoring.[13,14] Based on this evidence, the aim of the present study was to compare baseline impedance levels in patients with heartburn and pathophysiological characteristics related to FH divided into 2 groups on the basis of symptom relief after PPIs. Moreover, we compared these results with a group of patients with HE and healthy volunteers (HVs). Considering that impairment of chemical clearance is a primary pathophysiological mechanism specific to GERD,[15] our study secondly aimed to evaluate the efficacy of esophageal chemical clearance in the same 3 subgroups of patients, to correlate it with baseline impedance levels.

Materials and Methods

Throughout 2013, we prospectively enrolled a group of consecutive endoscopy-negative patients, with heartburn (with/without regurgitation), presenting to the outpatient motility laboratory at the Universities of Genoa, Pisa, Padua, and the Hospital of Modena (Italy).

The presence of erosive esophagitis and other abnormalities was excluded by upper endoscopy, performed in each earlier-listed Divisions of Gastroenterology within 6 months before the visit. Each patient discontinued PPIs or H2-receptor antagonists at least 20 days before undergoing endoscopy. After the first visit, a single dose of esomeprazole or pantoprazole 40 mg was prescribed to each patient for 8 weeks. Eighty-four patients were treated with esomeprazole and 36 patients were treated with pantoprazole. Symptoms were evaluated both before and after therapy through a validated questionnaire (GERD Impact Scale [GIS]) and a visual analogue scale (VAS) for heartburn as previously described.[8] Then, all subjects underwent stationary esophageal manometry and 24-hour MII-pH off-therapy (14-day wash-out). Patients were allowed to take only alginates, on an as-needed basis, as rescue therapy for

controlling heartburn.[16] The methodology of probe calibration, catheter placement, patient instruction, and performance was described previously.[1]

A group of 20 HVs, who never experienced GERD symptoms and/or took PPIs, underwent esophageal manometry and MII-pH off-therapy.

Multichannel Intraluminal Impedance and pH Monitoring Data Analysis

At the end of the recording period, MII-pH tracings were reviewed manually by 3 investigators (N.d.B., E.S., and M.F.) to ensure accurate detection and classification of reflux episodes and baseline impedance values. MII-pH data were used to determine the number and type of reflux episodes as well as AET in each patient. In particular, distal esophageal AET was defined as the total time with a pH if less than 4, divided by the total monitoring time. A total (24-h) percentage time the pH was less than 4 for less than 4.2% of the time was considered normal.[1,17] Acid, weakly acidic, and weakly alkaline refluxes were defined according to the previously published studies.[18] The proximal reflux extent was defined as a decrease in impedance recorded 15 cm from the lower esophageal sphincter. Finally, the correlation between symptoms and reflux events with the Symptom Index (SI) and the symptom association probability (SAP) was evaluated for each patient as previously described.[14]

Baseline impedance levels were assessed from the most distal channel ($z1$, 3 cm above the lower esophageal sphincter) during the overnight rest, at 3 time points, as previously described.[14] Moreover, for each patient, we assessed the chemical clearance according to the post-reflux swallow-induced peristaltic wave (PSPW) index.[15] The PSPW is defined as the number of refluxes followed within 30 seconds by a swallowing-induced peristaltic wave, divided by the number of total refluxes.

The Rome III criteria defined FH as the occurrence of chronic retrosternal burning in the absence of a GERD diagnosis (ie, negative endoscopy and pH monitoring) and the lack of response to acid-suppressive treatment.[4] According to endoscopy and MII-pH data, patients were included in the study in case of normal endoscopy, normal AET, and normal number of reflux episodes. Within this group, we enrolled both patients with a positive association between symptoms and refluxes based on a positive SI (if > 50%) and a positive SAP (if ≥ 95%) as previously described,[19] considered as affected by HE, and patients with a lack of association between symptoms and refluxes, thus suspected of having FH. Within the latter, we evaluated symptom relief after PPI therapy using GIS and VAS scores. Then, we stratified these patients into 2 groups by means of therapeutic outcome as follows: FH/PPI-responder, which consisted of 40 patients who reported satisfactory symptom relief for heartburn (>50% compared with baseline values);