Impedance-High Resolution Manometry Analysis of Patients With Nonerosive Reflux Disease

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BACKGROUND & AIMS: **Transient lower esophageal sphincter relaxations (TLESRs) contribute to episodes of reflux. Few studies have assessed the frequencies or compositions of TLESRs and reflux episodes in patients with reflux disease. We used combined high-resolution manometry and impedance monitoring to analyze reflux episodes and esophageal motility in these patients, compared with those of healthy individuals.**

METHODS: **We evaluated the frequency of TLESRs and the relationship between the reflux pattern and esophageal pressures during TLESRs in 14 patients with nonerosive reflux disease (NERD) and 11 controls. Study participants underwent combined high-resolution manometry and impedance monitoring before and 60 minutes after a solid and liquid meal. The diagnosis of NERD was confirmed by a 24-hour pH impedance test.**

RESULTS: **The frequency of TLESRs did not differ between patients with NERD and controls. In patients with NERD, TLESRs were associated more often with reflux episodes than in controls (93% ± 6% vs 66% ± 19%; $P < .05$). Patients with NERD had a higher percentage of pure liquid reflux episodes (33% ± 15% vs 10% ± 2%; $P < .05$), whereas controls had a higher percentage of mixed reflux episodes (45% ± 16% vs 67% ± 17% in patients with NERD; $P < .05$). Patients with NERD also had a higher percentage of reflux (liquid and mixed) associated with common cavities (74% ± 18% vs 50% ± 20% in controls; $P < .05$).**

CONCLUSIONS: **In contrast to previous studies, we found that TLESRs are associated more often with reflux in patients with NERD than control subjects; this association increases when only liquid and mixed refluxes are considered. These findings indicate that factors involved in the occurrence of reflux in patients with NERD during TLESRs are different from those in healthy subjects.**

Keywords: Esophagus; Acid; Reflux Episodes; Pressure Gradient; Gastroesophageal Junction.

Transient lower esophageal sphincter (LES) relaxations (TLESRs) are the most important mechanism leading to gastroesophageal reflux in patients with gastroesophageal reflux disease (GERD) as well as in healthy subjects.[1,2] Despite the relevance of TLESRs in the pathogenesis of GERD, relatively few studies have compared the frequency of TLESRs and reflux episodes, as well as their composition, in patients vs healthy subjects. Studies performed with conventional manometry showed that the frequency of reflux episodes and TLESRs are similar in GERD patients and in asymptomatic subjects.[3,4] However, in patients, TLESRs are associated more frequently with acid reflux,[3,5] probably as a consequence of the different position of the gastric acid pocket and/or a higher trans-sphincteric pressure gradient.[6,7]

Conventional manometry using a sleeve sensor at the gastroesophageal junction level has been considered, in the past few years, as the best technique to detect and analyze TLESRs, although its sensitivity in detecting these events has been questioned. With this technique, Dent[8] hypothesized that during prolonged periods of low LES resting pressure, as well as in periods of frequent swallowing, TLESRs may not be recognized. The recent development of esophageal high-resolution manometry (HRM) has enabled us to improve our knowledge regarding

Abbreviations used in this paper: AET, acid exposure time; GERD, gastroesophageal reflux disease; HRM, high-resolution manometry; LES, lower esophageal sphincter; MI, multichannel impedance; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; SAP, symptom association probability; TLESR, transient lower esophageal sphincter relaxation; TSPG, trans-sphincteric pressure gradient.

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esophageal motility and now is considered the gold standard in the study of esophageal motor disorders.[9] Indeed, HRM combined with multichannel impedance monitoring (HRM-MI) allows a simultaneous and more accurate analysis of the reflux episodes and esophageal motility. It recently was shown, in healthy subjects, that HRM is superior to sleeve manometry in the detection of TLESRs associated with reflux,[10] also providing a better interobserver agreement.[11] Furthermore, the combination of HRM with intraluminal impedance has been shown to discriminate reflux episodes associated with TLESRs better than those after swallow-induced LES relaxations.[11]

A study performed with HRM coupled with simultaneous fluoroscopy that investigated the esophageal motor events leading to esophagogastric junction opening during TLESRs in healthy subjects showed that esophageal shortening and inhibition of the crural diaphragm always occur before esophagogastric junction opening and the occurrence of a common cavity.[12] Moreover, it has been hypothesized that the longitudinal muscle contraction of the distal esophagus may represent the motor event leading to LES relaxation.[13]

The majority of the earlier-mentioned studies have been performed on asymptomatic subjects and, to our knowledge, no investigations using HRM and comparing the occurrence of TLESRs and the associated reflux episodes in GERD patients and healthy volunteers are available as yet. Furthermore, those previous studies were not focused on the relationship between the common cavity phenomenon and the reflux pattern during TLESRs. The present study, therefore, aimed to evaluate the frequency of TLESRs and the relationship between the reflux pattern and esophageal pressures during TLESRs in a consecutive series of patients with nonerosive reflux disease (NERD) and in healthy subjects, by means of HRM-MI.

Materials and Methods

Study Design

Participants were recruited from patients with nonerosive GERD who had been referred to our outpatient unit between December 2011 and November 2012. Selection criteria were as follows: (1) recurrent ($\geq$2/wk) typical GERD symptoms of heartburn and/or regurgitation, lasting for longer than 6 months and responding to proton pump inhibitors (PPIs) and (2) no evidence of erosive esophagitis at recent (within 2–6 weeks) or previous upper endoscopy performed after pharmacologic washout (>2 mo) from PPIs and/or H2-receptor antagonists.

Of 60 patients screened, 25 were eligible for the study. All 25 patients filled out a standardized structured questionnaire (Reflux Disease Questionnaire)[14] and underwent 24-hour ambulatory MI-pH monitoring; 14 patients (8 women; mean age, 39 y; range, 24–51 y) with NERD, as manifest by an abnormal acid exposure time (AET) and/or a positive symptom association probability (SAP) index, underwent combined HRM-MI. Besides a negative MI-pH test, the presence of predominant dyspepsia and evidence of a hiatal hernia larger than 2 cm were exclusion criteria.

Eleven asymptomatic healthy volunteers (6 women; mean age, 33 y; range, 20–48 y), matched for age, sex, and body mass index, served as controls and underwent MI-pH and the HRM-MI study. The volunteers were screened for reflux disease and any other significant diseases by interview and the Reflux Disease Questionnaire. The study was approved by the Ethics Committee of the University Campus Bio Medico of Rome and written informed consent was obtained from all individuals.

Multichannel Impedance–pH Monitoring

All subjects underwent preliminary stationary esophageal manometry to determine the location of the LES. The combined pH-impedance assembly (Sandhill Scientific, Highlands Ranch, CO) was positioned with the proximal pH electrode 5 cm above the LES. In this position, impedance was measured at 3, 5, 7, 9, 15, and 17 cm above the LES. Patients were asked not to lie down during the daytime, but only at their usual bedtime, and were instructed to have 3 meals and 2 beverages at fixed times. Event markers recorded occurrence of symptoms, times of meals, and changes in posture.

High-Resolution Manometry Multichannel Impedance

A catheter with 36 solid-state pressure sensors, located at 1-cm intervals, and 8 impedance measuring segments with a 2-cm separation (MMS; HRIM, Enschede, The Netherlands) was inserted, after an overnight fast, through a topically anesthetized nostril. The HRM-MI catheter was placed with at least 3 distal sensors positioned in the stomach and the distal impedance measuring segment at 5 cm above the LES, thus allowing an impedance recording at 5, 7, 9, 11, 13, 15, 17, and 19 cm above the LES. A preliminary manometric study, with ten 5-mL saline swallows, at 30-second intervals, was performed in each subject in a semirecumbent position. Subsequently, patients and controls were asked to eat a standardized, solid-liquid meal within 20 minutes (2 sandwiches with cheese, ham, and butter, 500 mL of still water, 1100 kCal). After the meal, HRM-MI recordings were continued for 1 hour, with subjects in a sitting position.

Data Analysis

24-Hour multichannel impedance–pH. Reflux events were detected and classified as liquid, mixed liquid–gas, and pure gas reflux episodes according to previously published criteria.[15] AET was defined as pathologic if the time at pH less than 4 exceeded 5% of the total recording time. The SAP for all reflux episodes was calculated according to the formula described elsewhere.[16] Both