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Alimentary Tract

Esophageal chemical clearance and baseline impedance values in patients with chronic autoimmune atrophic gastritis and gastro-esophageal reflux disease

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ABSTRACT

Background: The factors influencing new markers of gastro-esophageal reflux disease detected by impedance-pH monitoring – mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave (PSPW) index – need to be evaluated.
Aim: To compare endoscopy-negative heartburn with chronic autoimmune atrophic gastritis (CAAG).
Materials and methods: 24 patients with CAAG, 25 with non-erosive reflux disease (NERD) and 25 with functional heartburn (FH) were included. In all patients the main impedance-pH monitoring parameters were calculated.
Results: CAAG and NERD patients had a number of reflux events (non-acid ones being more common among the former group) which was higher than that found in FH ($p < 0.001$). MNBI decreased progressively in FH (>3000 Ohm), CAAG (>2000 Ohm) and NERD (<1000 Ohm) patients ($p = 0.0046$). The PSPW index was similar between CAAG and NERD patients but significantly lower in comparison to FH ($p < 0.0001$).
Conclusion: Patients with CAAG have evidence of non-acid reflux based on the high number of reflux events and confirmed by low values of MNBI and PSPW index. MNBI is a strong marker of acid/non-acid reflux-induced mucosal damage, whereas the PSPW index can reliably discriminate patients with reflux from those with FH, independently of the acidity of refluxate.

1. Introduction

Chronic autoimmune atrophic gastritis (CAAG) is a disease characterized by an immune-mediated loss of the parietal cells of the stomach resulting in hypo/achlorhydria [1]. The disease may lead to iron deficiency anemia and pernicious anemia [2]. These patients are frequently affected by upper gastrointestinal symptoms, such as dyspepsia, bloating or epigastric pain.

Recently Tenca et al. [3] described the prevalence of gastroesophageal reflux disease (GERD) in patients with CAAG. They observed that acid secretion has markedly decreased and acid reflux events are infrequent and, as a consequence, the PPI response is low. For this reason GERD diagnosis is frequently underestimated.

However, weakly acidic reflux episodes are known to give rise to symptoms, such as heartburn, regurgitation, or cough [4–6]. Still, upper digestive symptoms can be functional in CAAG patients and their development favored, on one side, by the low level of acid secretion (which would render the digestive process more diffi-

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cult) and, on the other, by anxiety, depression, or somatization [3,7] related to the patient's awareness about the risk of malignancy [8].

Esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring is considered as the gold standard for the evaluation of patients with GERD symptoms, since it can characterize the reflux episodes on the basis of their chemical composition (i.e., acid; Ac and non-acid; NA) [9] and it also allows the differentiation between patients affected by functional vs. organic disorder [10].

Recently, two novel impedance parameters evaluating esophageal chemical clearance and mucosal integrity, namely the post-reflux swallow-induced peristaltic wave (PSPW) index [11,12] and the mean nocturnal baseline impedance (MNBI) [13–15] have been proposed. After a reflux episode, esophageal clearance is primarily achieved by secondary peristalsis removing around 90% of the refluxate and elicited by stretch receptors in the esophageal lining (volume clearance). However, neutral esophageal pH is often restored only after voluntary swallowing is elicited by an esophago-salivary reflex mediated through vagal afferents and delivering salivary bicarbonate and epidermal growth factor (chemical clearance) [11]. According to previous findings, both the PSPW index and MNBI may be useful to increase the diagnostic sensitivity of MII-pH monitoring [12].

This study aimed at evaluating: (1) which factors affect MNBI and PSPW (i.e., acid and non-acid reflux) and (2) whether these parameters are useful in discriminating between patients with GERD vs. FH.

2. Material and methods

2.1. Study design

This is a multi-center retrospective observational analysis of MII-pH monitoring data.

2.2. Study protocol

During September 2015, data from three different prospective series [3,12] with specific clinical and MII-pH monitoring patterns were retrospectively reviewed. The three groups respectively comprised: 24 patients with CAAG and evidence of GERD on MII-pH monitoring study (named GERD-CAAG patients); 25 patients with heartburn diagnosed as NERD; and 25 patients with heartburn but no pathophysiological characteristics of GERD (functional heartburn, FH group).

All the subjects had undergone stationary esophageal manometry in order: (1) to determine the position of the lower esophageal sphincter (LES) by using the stationary pull-through technique [16,17] and (2) to exclude the presence of severe abnormalities of peristalsis and/or LES relaxation according to conventional manometry criteria (i.e., achalasia and scleroderma esophagus) [17]. Then, 24 h MII-pH esophageal monitoring off-therapy (i.e. wash-out from PPIs and histamine H2-receptor antagonists at least 10–14 days before the test) was performed as previously described [3,12]. During the wash-out period only alginates on an as-needed basis were allowed [18].

2.3. Patients

2.3.1. Patients with GERD-CAAG

In all the 24 patients, CAAG was diagnosed on the basis of the following criteria: (i) evidence of mainly body/fundus chronic gastritis with loss of gastric glandular cells and replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue, as evaluated according to the Sydney classification [19] in four samples of gastric mucosa (two taken from the antrum and two from the body of the stomach); (ii) hypergastrinemia and (iii) positive anti-parietal cells or intrinsic factor antibody in a blood sample. Additionally, any *H. pylori* infection was assessed in all the patients via the same histologic samples and eradicated when positive: its eradication was verified by urea breath test and it was successful in all of them. All the patients underwent a MII-pH monitoring study and the presence of GERD was defined as follows: (1) abnormal acid exposure time (AET) and/or increased number of total refluxes and/or a positive Symptoms Index (SI)/Symptom Association Probability (SAP) (see below "MII-pH monitoring analysis").

2.3.2. Patients with endoscopy-negative heartburn

The inclusion criteria for endoscopy-negative heartburn patients were: age older than 18 years; complaints of heartburn with/without regurgitation at least three times a week for 6 months in the previous year. The exclusion criteria were: pregnancy (excluded by urine analysis) and/or breast feeding, eating disorders, history of thoracic/esophageal/gastric surgery, underlying psychiatric illness or psychiatric therapies, use of non-steroidal anti-inflammatory drugs and aspirin, peptic ulcer or erosive esophagitis at previous endoscopy. The presence of erosive esophagitis and other mucosal abnormalities was excluded by means of upper endoscopy performed as off-therapy in one of the above-mentioned centers, within 6 months prior to the initial visit [20].

The patients were sub-grouped through pathophysiological examination performed by means of MII-pH as follows: (1) non-erosive reflux disease (NERD) patients: abnormal acid exposure time (AET); (2) functional heartburn (FH) patients: normal AET and total number of reflux events, absence of correlation between reflux events and symptoms over a 24 h MII-pH recording (SI and SAP) and absence of symptom relief during a previous proton pump inhibitor treatment.

2.4. MII-pH monitoring analysis

All tracings were blindly re-analyzed by expert observers (AT, NdB), with previous experience of analyzing at least 1000 tracings and performing at least 200 MII-pH monitoring instances/year. As the present study was conducted on subjects eating a Mediterranean diet, assessing normal MII-pH values referred to Italian normal values [21]. Impedance and pH data were used to determine the number and type of reflux episodes as well as an acid exposure time (AET, reflux percent time) in each patient. In particular, distal esophageal AET was defined as the total time with pH < 4, divided by the total time of monitoring. Then, a percent time lower than 4.2% with pH < 4 over 24 h, was considered as normal. In patients with CAAG the median gastric pH too was calculated. Reflux episodes were characterized on the basis of their chemical (i.e. acid vs. non-acid) and physical (i.e., liquid, gaseous and mixed-gaseous) composition, according to the Porto classification [22]. As weakly alkaline refluxes are very infrequent, they were merged with weakly acidic refluxes and considered as NA reflux. Only liquid and mixed liquid–gas reflux episodes according to impedance changes were included in the analysis. Proximal reflux was considered as reflux reaching a 15-cm impedance site [21,23]. In each patient, SIand SAPwere automatically calculated by software. Only the association between the principal symptom reported by the patient and Ac and NA reflux was reported. SI and SAP were defined according to Wiener et al. and Weusten et al., respectively [24,25] and considered as positive when ≥50% and when ≥95, respectively.

The PSPW index, previously described by Frazzoni et al. [11], was manually calculated and defined as the number of refluxes followed within 30 s by a swallow-induced peristaltic wave divided by the number of total refluxes. The MNBI value (in Ohm) was assessed through the same channel (5 cm above the LES) during the overnight rest, at three timepoints (around 1.00 a.m., 2.00 a.m.,

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