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Weakly acidic refluxes have a major role in the pathogenesis of PPI-resistant reflux oesophagitis.

Marzio Frazzoni¹, Rita Conigliaro², Gianluigi Melotti³

¹Fisiopatologia Digestiva - ²Gastroenterologia - ³Chirurgia Generale

Nuovo Ospedale S. Agostino - Modena - Italy

Corresponding author: Dr. Marzio Frazzoni - Fisiopatologia Digestiva –

Nuovo Ospedale S. Agostino - Viale Giardini 1355 - 41100 Modena – Italy -

Telephone/Fax: 0039/(0)59/3961201 e-mail m.frazzoni@ausl.mo.it

Short running title: Reflux in PPI-resistant reflux oesophagitis

Key words: Reflux oesophagitis - Acid reflux - Non-acid reflux - Proton pump inhibitors –

Competing interests: none to declare.

Summary

BACKGROUND

In patients with heartburn persisting despite proton pump inhibitor (PPI) therapy, reflux oesophagitis is rarely found and its pathogenesis has been scarcely studied.

AIM

To assess reflux parameters by impedance-pH monitoring in PPI-resistant reflux oesophagitis.

METHODS

Impedance-pH monitoring was performed on PPI therapy in patients with symptomatic reflux oesophagitis detected despite standard or high-dose PPI therapy of at least 8-week duration.

RESULTS

Twenty patients, ten on once daily and ten on twice daily PPI regimens, were studied. The gastric acid exposure time (percent time pH <4) ranged from 10% to 81% and was >30% in 70% of cases but the oesophageal acid exposure time (percent time pH <4) was abnormal in 20% of patients only. The number of acid, weakly acidic and weakly alkaline refluxes was abnormal in 25%, 100% and 15% of patients, respectively.

CONCLUSIONS

Weakly acidic refluxes were above the normal range in all cases whereas acid reflux parameters and weakly alkaline refluxes were normal in the vast majority of cases. Gastric acid secretion, with consequent intra-gastric pepsins activation, persists despite ongoing PPI therapy and activated pepsins may well be present in weakly acidic refluxes. As activated pepsins maintain their proteolytic activity in a weakly acidic environment, they may be responsible for mucosal damage. We conclude that weakly acidic refluxes have a major role in the pathogenesis of PPI-resistant reflux oesophagitis. **Therapeutic interventions in patients with PPI-resistant reflux oesophagitis should be tailored on the basis of impedance pH-monitoring results.**

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Introduction

Gastro-oesophageal reflux disease (GORD) has been defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the oesophagus (1). Reflux oesophagitis, defined by the presence of visible mucosal breaks at conventional endoscopic examination of the oesophagus (2), is diagnosed in a minority of untreated GORD patients and is the most common consequence of oesophageal injury due to acid reflux (3) rather than the principal manifestation of GORD (4). Currently, the diagnosis of GORD relies on troublesome heartburn with/without regurgitation, endoscopic evaluation being reserved to patients with alarm symptoms or typical symptoms unresponsive to PPI therapy (4,5).

Failure of proton pump inhibitor (PPI) therapy has become the most prevalent presentation of GORD in gastroenterology practice today. It is estimated that between 10% and 40% of patients with heartburn remain symptomatic on a standard dose of PPIs and many of them will continue to experience symptoms on even high doses of PPIs. Most of them originate from the group with non-erosive reflux disease (NERD) (6).

Impedance-pH monitoring is a new diagnostic tool that can reliably detect acid and non-acid refluxes off and on PPI therapy. By means of this new diagnostic tool, reflux symptoms persisting despite acid suppressive therapy have been associated with either acid or non-acid gastroesophageal reflux (7-9).

In patients with persisting typical reflux symptoms despite PPI therapy, upper endoscopy has been recommended (5) but reflux oesophagitis has rarely been found (10,11). Thus far, patients with reflux oesophagitis detected despite ongoing PPI therapy have not yet been prospectively studied with impedance-pH monitoring. It is therefore not known if reflux oesophagitis detected despite ongoing PPI therapy is associated with abnormal acid or non-acid reflux.

In this study, we assessed acid and non-acid reflux parameters by means of impedance pH-monitoring in patients with persisting heartburn and with reflux oesophagitis detected despite ongoing PPI therapy. Our aim was to establish whether abnormal acid and/or non-acid reflux parameters are associated with PPI-resistant symptomatic reflux oesophagitis.

Materials and methods

Patients

We prospectively studied patients aged 18-80 years who underwent upper gastrointestinal endoscopy at our open-access service. Standard criteria were adopted to evaluate and report oesophageal abnormalities. Reflux oesophagitis was defined according to the Los Angeles

classification (2). Hiatal hernia was defined as a distance between the diaphragmatic hiatus and the gastroesophageal junction >2 cm.

Patients with heartburn persisting despite at least 8 weeks of continuous standard/high-dose PPI therapy and in whom reflux oesophagitis was found at endoscopic examination were asked to participate to the study. All patients received comprehensible and detailed explanations and signed a written informed consent. Patients with peptic structures and progressive systemic sclerosis were excluded. The study protocol was approved by our Institutional Review Board. All patients continued the PPI regimen that they were on at the time of entering the study, i.e. 30 min before breakfast or 30 min before breakfast and before dinner for the once daily and the twice daily dosage regimen, respectively.

Oesophageal manometry

Standard oesophageal manometry was performed before impedance-pH monitoring in all patients (MF). The station pull-through method was used to locate the lower oesophageal sphincter (LOS). Briefly, an 8-channel, water perfused manometry catheter was placed nasally into the stomach and slowly withdrawn. The lower oesophageal sphincter (LOS) was identified, and then, at each 0.5-cm station the resting pressure was measured at the end of expiration and the relaxation was assessed with wet swallows. Oesophageal body peristalsis was assessed and pressures measured with at least ten wet swallows. The upper oesophageal sphincter was finally identified and the catheter removed. All manometric data were processed using the Polygram Net module (Medtronic Functional Diagnostics A/S, Tonsbakken, Denmark) in order to obtain the mean LOS tone and the mean distal oesophageal amplitude (DOA).

Impedance-pH monitoring

Impedance-pH monitoring, always preceded by standard oesophageal manometry, was performed on PPI therapy (MF). An ambulatory, multi-channel, intra-luminal impedance system was used, consisting of a portable data logger and a combined impedance-pH catheter (Sleuth ambulatory system, Sandhill Scientific, Inc; Highland Ranch, CO). After LOS location by oesophageal manometry, the impedance-pH catheter was passed trans-nasally. The configuration of the catheter adopted allowed monitoring changes in intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm above the LOS upper border. In addition, pH was monitored at 5 cm above and 10 cm below the LOS upper border. Subjects were discharged and were encouraged to maintain normal activities, sleep schedule, and eat their usual meals at their normal times. They were asked to remain upright during the day, and lie down only during their usual nocturnal bedtime. Event markers on the data-

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3 logger recorded symptoms, meal times, and posture changes. All studies were performed for 24 h,
4 after which patients returned to the lab for catheter removal and data review. Impedance, pH, and
5 symptom signals were collected at a resolution of a 50-Hz sampling rate on a 256-MB compact
6 flash card for later download. Impedance and pH information was analysed using a dedicated
7 software program (BioView Analysis, Sandhill Scientific, Inc; Highland Ranch, CO) and visual
8 analysis (MF). Analysis included identification, enumeration and characterization of individual
9 reflux events and their relationship with symptoms. Meal times were excluded. Liquid-only reflux
10 was defined as a retrograde 50% fall in impedance from baseline in the two distal impedance sites.
11 Gas reflux was defined as a rapid increase in impedance >3,000 ohms, occurring simultaneously at
12 least in two oesophageal measuring segments. Liquid–gas (mixed) reflux was defined as gas reflux
13 occurring immediately before or during a liquid reflux. Gas reflux events without liquid (belches)
14 were considered separately and not included in the analysis. The time period with gastric pH < 4,
15 i.e. the percentage gastric acid exposure time (GAET), was computed for the total study period as
16 well as the time period with oesophageal pH < 4, i.e. the percentage oesophageal acid exposure time
17 (OAET). Using the pH tracings, reflux events were classified as: i) acid (nadir pH<4), ii) weakly
18 acidic (nadir pH between 4 and 7) or iii) weakly alkaline (nadir pH not below 7) refluxes (12). Data
19 analysis was performed on liquid and mixed reflux episodes for acid, weakly acidic and weakly
20 alkaline refluxes in the distal oesophagus. The number of proximal reflux events (reaching the 15-
21 cm impedance site) was also assessed. The 95th percentile of values obtained in 20 healthy controls
22 studied in the same way at our centre (13) served as the upper normal limit.

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41 **Statistics**

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43 Reflux parameters were expressed as the median and interquartile range. Correlation
44 between GAET and OAET was assessed using the Spearman rank correlation test. To analyse the
45 differences between patients on once daily and twice daily PPI regimens, the Mann-Whitney test
46 and the Fisher’s exact test were used as appropriate. A *P* <0.05 was considered significant.

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52 **Results**

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55 Between March 2007 and September 2010, 20 patients with persisting heartburn and reflux
56 oesophagitis detected despite ongoing PPI therapy of at least 8-week duration were studied. Their
57 baseline characteristics are reported in Table 1; the LOS tone was lower than 10 mmHg in 7 (35%)
58 cases.
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The median GAET was 38% (range 10%-81%); it was >30% in 14 (70%) patients. There was no significant correlation between the GAET and the OAET ($r_s = 0.072$, P NS).

The median and interquartile range of the main reflux parameters are reported in Table 2. The OAET was higher than normal in 4 (20%) patients; the number of acid, weakly acidic and weakly alkaline refluxes was above the normal range in 5 (25%), 20 (100%) and 3 (15%) patients, respectively (Figure 1).

Ten patients were on a once daily regimen and ten patients were on a twice daily regimen of their particular PPI. The GAET was >30% in eight (40%) patients on a once daily regimen and in six (30%) patients on a twice daily regimen (P NS). Median values of GAET and reflux parameters did not differ significantly between the two subgroups of patients (Table 3).

Discussion

In this study, we prospectively assessed acid and non-acid reflux parameters in patients with persisting heartburn and with reflux oesophagitis detected despite ongoing assumption of a standard/high-dose PPI therapy from at least 8 weeks. We found abnormal acid and weakly alkaline reflux parameters in a small minority of patients whereas the number of weakly acidic refluxes was above the normal range in all cases.

Healing of mucosal lesions in reflux oesophagitis represents a reliable end point for success of therapy and correlates well with improvement of heartburn (4). Ninety percent healing rates have been reported with standard PPI dosages after 8 weeks of treatment (14). Accordingly, in a recent study reflux oesophagitis has been detected in less than 7% of patients with persisting heartburn despite PPI treatment (11), a result confirming that the vast majority of PPI-unresponsive GORD patients belong to the NERD group (6).

Healing of reflux oesophagitis has been positively related to the percentage of time intra-oesophageal (15) and intra-gastric pH (16) are >4. Recently, maximal reflux oesophagitis healing rates have been related to an intra-gastric pH >4 for 70% or more of the 24-h period: intra-gastric pH control has then been proposed as a clinically relevant measurement of drug efficacy in the treatment of patients with moderate to severe reflux oesophagitis (17). In our patients, one half of whom treated with a standard PPI dosage, an intra-gastric pH >4 was achieved for 70% of the time in only 30% of cases as a GAET >30% was detected in 70% of cases. However, the OAET and the number of acid refluxes were above the normal range only in 20% and 25% of cases, respectively: these findings are to be related to the lack of correlation between GAET and OAET ($r_s = 0.072$, P

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NS), in accordance with previous studies (13,18), and confirm the multi-factorial pathogenesis of GORD.

As we found a higher than normal number of weakly acidic refluxes in all our patients, we believe that weakly acidic refluxes have a relevant role in the pathogenesis of PPI-resistant reflux oesophagitis. Reflux oesophagitis was originally termed “peptic” (19), i.e. an oesophagitis resulting from the irritant action on the mucosa of hydrochloric acid and pepsins. Indeed, the presence of pepsins is critical for oesophageal mucosal damage to occur: activation of these proteolytic enzymes occurs at $\text{pH} < 4.5$, proteolytic activity is maintained up to $\text{pH} 5.5$ and denaturation occurs at $\text{pH} > 7$ (20). We considered separately weakly acidic refluxes from weakly alkaline refluxes as peptic mucosal damage would not be expected when reflux occurs at a $\text{pH} > 7$. Weakly alkaline refluxes were above the normal range in a small minority (15%) of cases only. Therefore, we believe that weakly alkaline refluxes have a little role, if any, in the pathogenesis of reflux oesophagitis. On the other hand, as the lowest GAET value that we detected was 10% and as in 70% of our patients the GAET was $>30\%$, activation of pepsins may have well occurred in the stomach of all our patients, both those on once daily as well as those on twice daily PPI therapy. Therefore, activated pepsins may have been present in a relevant proportion of weakly acidic refluxes detected in our patients, proteolytic activity being maintained when the pH was <5.5 . As we found a higher than normal number of weakly acidic refluxes in all our patients, presence of activated pepsins in a weakly acidic oesophageal environment during reflux episodes may represent the main pathogenic mechanism by which visible oesophageal mucosa damage may be found in some GORD patients despite ongoing PPI therapy. Our results confirm that weakly acidic reflux is one of the major underlying mechanisms of refractory GORD (21).

Despite one half of our patients were on a once daily PPI regimen, we found abnormal acid reflux parameters in a minority of them and independently of the PPI dosage schedule. **Therefore, we agree that treating patients on the basis of impedance-pH monitoring results rather than treating them empirically will result in increased treatment success** (22). However, impedance-pH monitoring should include oesophageal as well as gastric pH monitoring, as the efficacy of incremental PPI dosages for those patients (30% of cases in our series) with a GAET $<30\%$ would probably be low (17). Recently, we have shown that laparoscopic fundoplication improves significantly symptoms as well as acid and weakly acidic reflux parameters when compared with high-dose PPI therapy in refractory GORD patients (9). Our findings support the view that therapeutic interventions in PPI-resistant GORD with/without reflux oesophagitis should be guided by impedance-pH monitoring, in order to identify those patients who would benefit more from laparoscopic fundoplication than from incremental PPI dosages (23).

The vast majority of our patients were males, as expected in patients with reflux oesophagitis (24), and had a hiatal hernia which adversely affects the efficacy of PPI therapy (25). As our patients had active reflux oesophagitis, basal impedance was sometimes low in our series, but we confirm that this does not preclude the recognition of reflux episodes during visual analysis (12,13). Our upper normal limits, defined by the 95th percentile of values obtained in 20 healthy controls at our centre (13) are at variance with those reported by previous series (26,27). This can be explained by different dietary habits: our normal values were obtained in normal subjects eating their usual meals in a Mediterranean region and are very close to those found in our country when a standardized Mediterranean diet was adopted (28). Moreover, there is evidence that the OAET is lower when impedance-pH instead of pH-only criteria are adopted to detect acid reflux (29).

In conclusion, we have found that in patients with persisting heartburn and with reflux oesophagitis detected despite ongoing PPI therapy, weakly acidic refluxes were above the normal range in all cases whereas acid reflux parameters and weakly alkaline refluxes were normal in the vast majority of cases. We have shown that gastric acid secretion, with consequent intra-gastric pepsins activation, may persist despite ongoing PPI therapy: activated pepsins may well be present in a relevant proportion of weakly acidic refluxes. As activated pepsins maintain their proteolytic activity in a weakly acidic environment, they may be responsible for mucosal damage. We conclude that weakly acidic refluxes have a major role in the pathogenesis of PPI-resistant reflux oesophagitis. Therapeutic interventions in patients with PPI-resistant reflux oesophagitis should be tailored on the basis of impedance pH-monitoring results.

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Table 1. Baseline characteristic of 20 patients with symptomatic reflux oesophagitis detected on PPI therapy

Age (years) (median) (IQR)	44 (36-58)
Male gender (n) (%)	17 (85%)
Hiatal hernia (n) (%)	16 (80%)
Grade A reflux oesophagitis (n) (%)	7 (35%)
Grade B reflux oesophagitis (n) (%)	11 (55%)
Grade C reflux oesophagitis (n) (%)	2 (10%)
LOS tone (mmHg) (median) (IQR)	11.6 (8.2-18.8)
DOA (mmHg) (median) (IQR)	64.6 (47.5-93.5)

IQR = interquartile range

LOS = lower oesophageal sphincter

DOA = distal oesophageal amplitude

Table 2. Twenty-four-hour impedance-pH monitoring values in 20 patients with symptomatic reflux oesophagitis detected on PPI therapy

	Median (interquartile range)	Upper normal limit
OAET (%)	0.8 (0.3-2.3)	3,3
Acid refluxes (n)	15 (5-21)	23
Weakly acidic refluxes (n)	73 (52-94)	27
Weakly alkaline refluxes (n)	0 (0-0)	2
Distal reflux events (n)	89 (71-108)	45
Proximal reflux events (n)	50 (34-76)	32

OAET = oesophageal acid exposure time

Table 3. Twenty-four-hour impedance-pH monitoring values in 20 patients on once daily or twice daily PPI therapy

	Once daily regimen (10 patients)	Twice daily regimen (10 patients)
GAET (%)	38 (31-47)	39 (26-55)
OAET (%)	0.7 (0.2-2)	0.9 (0.4-2.3)
Acid refluxes (n)	7 (3-19)	18 (12-22)
Weakly acidic refluxes (n)	73 (49-95)	65 (54-92)
Weakly alkaline refluxes (n)	0 (0-2)	0 (0-0)
Distal reflux events (n)	80 (67-9125)	90 (74-101)
Proximal reflux events (n)	61 (38-86)	47 (33-65)

Values are expressed as median (interquartile range).

P NS for all comparisons.

GAET = gastric acid exposure time

OAET = oesophageal acid exposure time

Figure 1

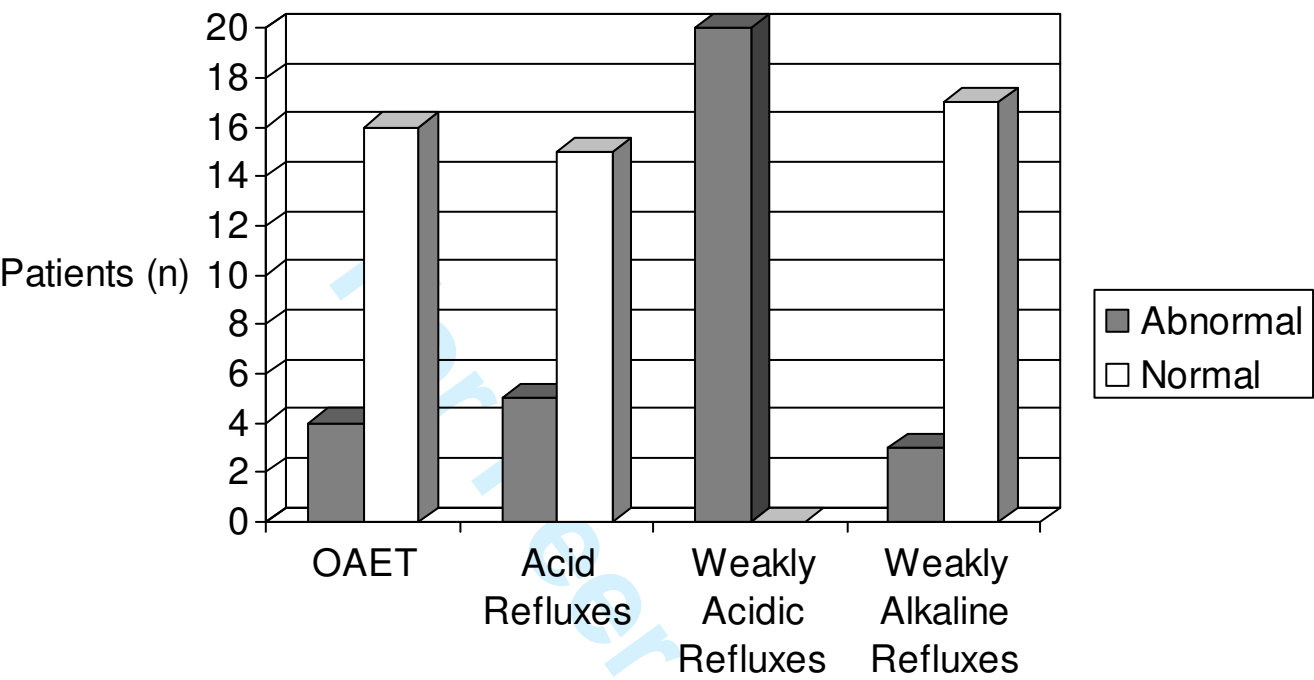


Figure legend

Figure 1. Abnormal and normal reflux parameters in 20 patients with symptomatic reflux oesophagitis detected on PPI therapy

OAET = oesophageal acid exposure time

For Peer Review

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Statement of interests

There are no affiliations that might lead to bias or a conflict of interest.

For Peer Review