ORIGINAL ARTICLE

Clinical, but not oesophageal pH-impedance, profiles predict response to proton pump inhibitors in gastro-oesophageal reflux disease

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ABSTRACT

Objective Approximately 30% of patients with gastro-oesophageal reflux disease (GORD) do not achieve adequate symptom control with proton pump inhibitors (PPIs). The aim of this study was to determine whether any symptom profile or reflux pattern was associated with refractoriness to PPI therapy.

Design Patients with typical GORD symptoms (heartburn and/or regurgitation) were included and had 24 h pH-impedance monitoring off therapy. Patients were considered to be responders if they had fewer than 2 days of mild symptoms per week while receiving a standard or double dose of PPI treatment for at least 4 weeks. Both clinical and reflux parameters were taken into account for multivariate analysis (logistic regression).

Results One hundred patients were included (median age 50 years, 42 male), 43 responders and 57 non-responders. Overall, multivariate analysis showed that the factors associated with the absence of response were absence of oesophagitis (p=0.050), body mass index (BMI) $\leq$25 kg/m^2 (p=0.002) and functional dyspepsia (FD) (p=0.001). In patients who reported symptoms during the recording (n=85), the factors associated with PPI failure were BMI $\leq$25 kg/m^2 (p=0.004), FD (p=0.009) and irritable bowel syndrome (p=0.045). In patients with documented GORD (n=67), the factors associated with PPI failure were absence of oesophagitis (p=0.040), FD (p=0.003), irritable bowel syndrome (p=0.012) and BMI $\leq$25 kg/m^2 (p=0.029).

Conclusion No reflux pattern demonstrated by 24 h pH-impedance monitoring is associated with response to PPIs in patients with GORD symptoms. In contrast, absence of oesophagitis, presence of functional digestive disorders and BMI $\leq$25 kg/m^2 are strongly associated with PPI failure.

Significance of this study

What is already known about this subject?
- Up to 40% of patients with gastro-oesophageal reflux disease (GORD) have inadequate symptom relief.
- Absence of oesophagitis (non-erosive reflux disease) and normal 24 h acid exposure are associated with proton pump inhibitor (PPI) failure in patients with GORD.
- Functional digestive disorders are often associated with GORD.

What are the new findings?
- No reflux pattern associated with PPI failure can be demonstrated by 24 h pH-impedance monitoring performed off therapy.
- Body mass index (BMI) $\leq$25 kg/m^2 is a crucial factor of inadequate response to PPIs.
- Functional digestive disorders are independent factors of PPI failure even in patients with documented GORD.

How might it impact on clinical practice in the foreseeable future?
- BMI and presence of functional digestive disorders should be assessed in patients with GORD symptoms and used as predictors of response to PPI therapy.
- The presence of functional digestive disorders should be taken into account in future trials with reflux inhibitors.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a common disorder caused by the reflux of gastric contents into the oesophagus. The pivotal role of the acid component of the refluxate is demonstrated by the remarkable efficacy of acid-suppressive therapies in both mucosal healing and symptom relief.[1] However, a subgroup of patients with GORD is refractory to acid-suppressive therapy, and, although there is no widely admitted definition of 'refractoriness' to proton pump inhibitors (PPIs), it is generally admitted that up to 40% of patients have inadequate symptom relief after a 4-week course of a single dose of PPI.[1 2]

Non-erosive reflux disease (NERD) is a GORD phenotype that has been clearly associated with lower response to PPI in several studies.[3–5] In a systematic review of the literature, Dean *et al* reported pooled response rates at 4 weeks to be significantly higher for patients with erosive oesophagitis than for those with NERD (56% vs 37%, p<0.0001).[3] Patients with GORD often have functional digestive disorders[6 7] that may also influence the response to therapy, although very few data are currently available.[8]

The underlying mechanisms involved in PPI failure are best assessed by ambulatory reflux monitoring. Hence, studies with 24 h pH monitoring have shown that patients with normal

acid exposure have the lowest rate of response to PPIs.[9 10] Ambulatory 24 h pH studies can also demonstrate a positive symptom–reflux association (ie, symptom index (SI)[11] and symptom association probability (SAP)[12]), which has been associated with a better response to PPIs.[9 13 14] The subgroup of patients with the so-called acid-hypersensitive oesophagus is characterised by a normal oesophageal acid exposure and a positive symptom association, thus reflecting an underlying visceral hypersensitivity.[2] These patients usually have NERD and very often dyspeptic-associated symptoms.[15 16] Compared with pH-alone monitoring, combined oesophageal pH-impedance monitoring allows detection and characterisation of all types of reflux episodes as well as their extent to the proximal oesophagus.[17] Using this technology, it has been shown that symptoms that persist while the patient is receiving PPIs are often associated with weakly acidic reflux events.[18 19] Moreover, reflux events with high proximal extent are more likely to be symptomatic in patients either off[20] or on[21 22] PPI therapy. However, pH-impedance monitoring has never been used to assess the reflux patterns that are associated with PPI failure.

Therefore the aim of this study was to determine clinical profiles and GOR patterns associated with PPI failure using 24 h pH-impedance monitoring off PPI.

PATIENTS AND METHODS

Study design and patients

We conducted a study in three university hospitals (Bordeaux, Nantes and Lyon) in consecutive patients referred for 24 h pH-impedance monitoring off therapy. All patients presented with typical GORD symptoms—that is, regurgitation and/or heartburn—as the predominant symptoms. Regurgitation was defined as the sensation of effortless return of gastric or oesophageal fluid into the mouth or throat; heartburn was defined as a burning and ascending retrosternal sensation.

Patients were considered to be responders to PPI therapy if they had fewer than 2 days of mild symptoms per week while receiving a standard or double dose of PPI treatment for at least 4 weeks. Responders were referred for pH-impedance monitoring as a preoperative workup before surgery. There were also patients referred for refractory symptoms that appeared to be adequately controlled after treatment optimisation (increased dose, change of PPI, dosing time) and therefore considered to be responders. Some responders had received pH-impedance monitoring off PPI as baseline assessment in a pharmacological clinical trial.

Patients were considered to be non-responders if they had more than 2 days of mild symptoms per week while receiving a standard or double dose of PPI treatment for at least 4 weeks. Non-responders were referred for 24 h pH-impedance monitoring in order to demonstrate the presence of pathological GOR.

Exclusion criteria were: grade C/D oesophagitis; history of thoracic, oesophageal or gastric surgery; primary or secondary severe oesophageal motility disorders (eg, achalasia, scleroderma).

Endoscopy and clinical assessment

For all patients, demographic data were collected, including height and weight to determine body mass index (BMI). Endoscopy was not performed systematically, but the results of previous endoscopies were taken into account. The presence of associated functional dyspepsia (FD) and/or irritable bowel syndrome (IBS) was determined according to the Rome III classification using a standardised questionnaire.

Impedance-pH monitoring

Oesophageal impedance-pH monitoring was performed using a Sleuth Multi-channel Intraluminal Impedance ambulatory system (Sandhill Scientific, Highland Ranch, Colorado, USA). The system includes a portable data-logger with impedance-pH amplifiers and a catheter containing one antimony pH electrode and eight impedance electrodes at 2, 4, 6, 8, 10, 14, 16 and 18 cm from the tip of the catheter. Each pair of adjacent electrodes represents an impedance-measuring segment, 2 cm in length, corresponding to one recording channel. The impedance amplifier delivers AC voltage in a range of 1–2 kHz with resulting current flow variations in response to intraluminal impedance changes. The six impedance and pH signals were recorded at 50 Hz on a 128 MB CompactFlash card for further analysis.

The studies were performed on an outpatient basis after an overnight fast and withdrawal of PPIs (or any antisecretory therapy) at least 7 days before the recording. Before the start of the recordings, the pH recorder was calibrated using pH 4.0 and pH 7.0 buffer solutions.

After lower oesophageal sphincter (LOS) location by oesophageal manometry, the impedance-pH catheter was passed transnasally under topical anaesthesia and positioned in the oesophageal body to record pH at 5 cm and impedance at 3, 5, 7, 9, 15 and 17 cm proximal to the LOS.

Subjects were discharged and were encouraged to maintain normal activities and sleep schedule and eat their usual meals at the normal times. They were asked to remain upright during the day and lie down only during their usual bedtime. Event markers on the data-logger recorded symptoms, meal times and posture changes.

The data stored on the CompactFlash card were downloaded on to a personal computer and visually analysed using dedicated software (Bioview Analysis, version 5.0.9; Sandhill Scientific). Analysis included identification, enumeration and characterisation of individual reflux events and measuring clearance times (bolus and pH clearance). Meals were excluded for the analysis.

Definitions of reflux episodes

Liquid reflux was defined as a retrograde 50% fall in impedance starting distally (at the level of the LOS) and propagating to at least the next two more proximal impedance measuring segments. Only liquid reflux episodes lasting at least 3 s were taken into account. Gas reflux was defined as a rapid (3 kΩ/s) increase in impedance >5000 Ω, occurring simultaneously at least in two oesophageal measuring segments, in the absence of swallowing. Mixed liquid/gas reflux was defined as gas reflux occurring immediately before or during a liquid reflux. Gas reflux events without liquid (belches) were not considered for the purpose of this study. Reflux episodes were characterised by pH-metry as acidic, weakly acidic, or weakly alkaline according to a consensus report on detection and definitions of GOR[17]:

1. acid reflux: refluxed gastric juice with a pH less than 4 which can either reduce the pH of the oesophagus to below 4 or occur when oesophageal pH is already below 4;
2. weakly acidic reflux: reflux events that result in an oesophageal pH between 4 and 7;
3. weakly alkaline reflux: reflux episodes during which nadir oesophageal pH does not fall below 7.

GOR variables

All reflux events were analysed with the patient in both upright and supine positions, and the following variables were obtained from the impedance and pH recordings: total oesophageal acid exposure (%); number of reflux episodes (acid, weakly acidic);

bolus exposure (reflux percentage time); number of reflux events with proximal extent (reflux reaching 15 cm impedance site). Considering that weakly alkaline reflux events were extremely rare in patients not receiving PPIs,[19] these reflux events were not taken into account for the analysis.

Each variable was considered to be normal or abnormal compared with normal values obtained by our group in 72 healthy subjects studied in ambulatory conditions with non-standardised meals.[23] The 95th centile values obtained in this series were considered to be the upper limit of normal values.

Symptom–reflux association analysis

The symptom–reflux association analysis was performed using both SI[11] and SAP.[12] Separate analysis was performed for each individual symptom if patients recorded different types of symptoms. SI and SAP were calculated for acid and weakly acid reflux using dedicated software (gift from Dr Radu Tutuian). Symptoms were considered to be related to reflux if they occurred within a 2 min time window after the onset of the reflux episode. A positive SI (SI+) was declared if ≥50%; SAP was considered positive if ≥95%. Patients were considered to have positive symptom–reflux association if they had positive SI or SAP.

Statistical analysis

All demographic, clinical and GOR variables were compared between responders and non-responders. Comparisons were performed using the χ^2 or Fisher exact test when appropriate. All variables with a p value <0.10 in univariate analysis were entered into a multivariate logistic regression model. A p value <0.05 was considered significant. The statistical analysis was performed in the whole population. Additional statistical analysis was performed in two different subgroups according to different criteria based on 24 h pH-impedance monitoring: patients with symptoms reported during the 24 h pH-impedance monitoring, and patients with documented acid GORD (ie, abnormal 24 h acid exposure and/or positive symptom–reflux association).

RESULTS

Patients

A total of 100 patients were included, 58 female, median age 50 years (IQR 19–81). Demographic, clinical and GOR characteristics of the population are summarised in tables 1 and 2. The median BMI of the population was 24.1 (IQR 22.0–27.5). Thirty-eight patients were overweight (BMI >25 kg/m^2) and 16 were obese (BMI ≥30 kg/m^2). There was a high prevalence of FD and IBS (48% and 36%, respectively) in the study population; only 14% had a history of oesophagitis. Thirty-five per cent of patients had an abnormal 24 h oesophageal acid exposure, and 46% had an abnormal 24 h oesophageal bolus exposure. Only 10% of patients had an oesophageal acid exposure >10%. A positive symptom–reflux association analysis was found in 47% and 50% of patients with SAP and SI, respectively. There were 56 patients with NERD (ie, no oesophagitis, 24 h oesophageal acid exposure >5% and/or positive symptom–reflux association analysis), and 16 patients with functional heartburn (no oesophagitis, normal 24 h oesophageal acid exposure and negative symptom–reflux association analysis).

Overall, 43 patients were considered to be PPI responders according to our definition (77% and 23% on single and double dose of PPIs, respectively), and 57 were considered to be non-responders (37% and 62% on single and double dose of PPIs, respectively) (table 1). The response rate in oesophagitis, NERD and functional heartburn were 71.4% (10/14), 39.3% (22/56) and 25.0% (4/16) (p=0.029), respectively.

Factors associated with inadequate response to PPIs

Whole population

In the whole population (n=100), the univariate analysis demonstrated that female gender, BMI ≤25 kg/m^2, absence of oesophagitis, normal oesophageal acid exposure, normal 24 h oesophageal bolus exposure, and FD were significantly associated with inadequate response to PPIs (tables 1 and 2). Prevalence of IBS was also increased in non-responders, but failed to reach the level of significance (p=0.059). The percentage of patients with positive symptom–reflux association analysis (either SI or SAP positive for any symptom or type of reflux) was similar in responders and non-responders (72% and 66% respectively, NS). Similar results were found when each test (SI, SAP), type of reflux (acid, weakly acidic) or symptom (heartburn, regurgitation) was studied separately (table 2). Other cut-offs of oesophageal acid exposure (percentage time with pH <4 above 10% and 15%) were tested and were not associated with response to PPIs.

In the multivariate analysis, the factors associated with inadequate response were BMI ≤25 kg/m^2 (p=0.002), FD (p=0.001) and absence of oesophagitis (p=0.050) (table 3).

Patients with symptoms during 24 h pH-impedance monitoring

In patients who reported symptoms during the 24 h pH-impedance monitoring (n=85), the univariate analysis showed that female gender (p=0.028), BMI ≤25 kg/m^2 (p=0.001), FD (p<0.001), IBS (p=0.008) and normal 24 h oesophageal acid exposure (p=0.044) were associated with inadequate response to PPI. The percentage of patients with positive SI was similar in responders and non-responders (65.6% vs 54.7%, respectively, p=0.322). Similar results were found for SAP (59.4% vs 52.8%, respectively, p=0.557). The percentage of patients with either positive symptom–reflux association analysis or oesophageal acid exposure >5% was higher in responders than

Table 1 Clinical and demographic characteristics of the study population (univariate analysis)

Characteristic	Whole population (n=100)	Responders (n=43)	Non-responders (n=57)	p Value
Age, years*	50 (38–61)	49 (33–61)	51 (41–61)	0.371
Male/female, n	42/58	24/19	18/39	0.015
BMI >25 kg/m^2, (%)	38	25 (58.1)	13 (22.8)	<0.001
Oesophagitis, n (%)	14 (14.0)	10 (23.0)	4 (7.0)	0.021
Functional dyspepsia, n (%)	48 (48.0)	11 (25.6)	37 (64.9)	<0.01
Irritable bowel syndrome, n (%)	36 (36.0)	11 (25.6)	25 (43.9)	0.059
PPI dose single/double, %	54/46	77/23	37/63	<0.001

*Median (IQR).
BMI, body mass index; PPI, proton pump inhibitor.

Table 2 Characteristics of the study population receiving 24 h pH-impedance monitoring

Reflux variable (upper limit of normal value)*	Whole population (n=100)	Patients with abnormal values (%)		p Value
		Responders (n=43)	Non-responders (n=57)	
Acid exposure 24 h (5.0%)	3.1 (1.0–6.6)	20 (46.5)	15 (26.3)	0.036
Bolus exposure 24 h (2.0%)	1.8 (0.9–2.6)	25 (58.1)	21 (36.8)	0.034
Total reflux events 24 h (n=75)	56 (37–73)	10 (23.3)	10 (17.5)	0.480
Acid reflux events 24 h (n=50)	39 (22–53)	15 (34.9)	14 (24.6)	0.260
WAR events 24 h (n=33)	12 (8–21)	4 (9.3)	7 (12.3)	0.753
Reflux with HPE (n=30)	27 (16–40)	20 (46.5)	22 (38.6)	0.427
SAP positive for acid reflux	43	19 (59.4)	24 (45.3)	0.208
SI positive for acid reflux	46	20 (64.5)	26 (50.0)	0.198
SAP positive for WAR	13	4 (13.3)	9 (17.3)	0.760
SI positive for WAR	5	2 (6.5)	3 (5.7)	1.000
SAP positive (acid/weakly acidic)	47	19 (59.4)	28 (52.8)	0.557
SI positive (acid/weakly acidic)	50	21 (65.6)	29 (54.7)	0.322
SI or SAP positive	58	23 (71.9)	35 (66.0)	0.575

Values are median (IQR) or number (%).
*Normal values were established previously in 73 healthy subjects.[23]
HPE, high proximal extent; SI, symptom index; SAP, symptom association probability; WAR, weakly acidic reflux.

non-responders, but failed to reach the level of statistical significance (81.2% vs 69.8%, p=0.243).

In the multivariate analysis, the only factors associated with inadequate response were BMI ≤25 kg/m^2 (p=0.004), FD (p=0.009) and IBS (p=0.044) (table 3).

Patients with documented GORD on pH-impedance monitoring

In patients with abnormal 24 h oesophageal acid exposure (>5%) and/or positive symptom–reflux association analysis (n=67)—that is, with documented pathological acid GOR—the univariate analysis showed that female gender (p=0.006), BMI ≤25 kg/m^2 (p=0.018), FD (p<0.001), IBS (p=0.004) and 24 h oesophageal acid exposure <5% (p=0.033) were associated with inadequate response to PPIs.

In the multivariate analysis, the factors associated with inadequate response were FD (p=0.003), BMI ≤25 kg/m^2 (p=0.029), IBS (p=0.012) and absence of oesophagitis (p=0.040) (table 3).

DISCUSSION

The most striking observation in the present study is that no reflux pattern on 24 h pH-impedance monitoring performed off therapy is predictive of response to PPI therapy in GORD. In contrast, it was observed that PPI failure is mainly associated with BMI ≤25 kg/m^2 and presence of functional digestive disorders, even when pathological GOR can be demonstrated by 24 h pH-impedance monitoring.

Table 3 Independent predictive factors of PPI failure in three groups of patients with gastro-oesophageal reflux symptoms (multivariate analysis)

Factor	OR (95% CI)	p Value*
Whole population (n=100)		
BMI ≤25 kg/m^2	5.33 (1.88 to 15.07)	0.002
Functional dyspepsia	5.61 (1.99 to 15.79)	0.001
No oesophagitis	4.19 (1.00 to 17.64)	0.050
Patients with symptoms (n=85)		
BMI ≤25 kg/m^2	5.03 (1.66 to 15.23)	0.004
Functional dyspepsia	4.46 (1.46 to 13.68)	0.009
Irritable bowel syndrome	3.65 (1.03 to 12.98)	0.044
Patients with documented GORD (n=67)		
Functional dyspepsia	7.95 (2.00 to 31.60)	0.003
No oesophagitis	6.96 (1.09 to 44.30)	0.040
Irritable bowel syndrome	6.51 (1.51 to 28.08)	0.012
BMI ≤25 kg/m^2	4.51 (1.17 to 17.38)	0.029

Patients with documented GORD had 24 h oesophageal acid exposure >5% and/or positive SI/SAP.
*Logistic regression.
BMI, body mass index; GORD, gastro-oesophageal reflux disease; PPI, proton pump inhibitor.

This study was performed in a population of patients that can be considered to be representative of patients presenting with typical GORD symptoms: low proportion of patients with reflux oesophagitis (14%), high prevalence of overweight (36%) and associated functional disorders (48% with FD and 36% with IBS).[7 8 24 25] Most responders (77%) to PPI were receiving a daily single dose, while the majority of patients (62%) refractory to therapy were receiving a double dose of PPIs, which is very common in France. There were only 35% of patients with abnormal 24 h oesophageal acid exposure, but as a whole, 67% of patients had documented abnormal GOR defined by either abnormal oesophageal acid exposure or positive symptom–reflux association analysis. Therefore one could argue that this population did not present with severe GORD, but with either NERD or hypersensitive oesophagus. Although there are no specific studies to support this assumption, we believe that it is nowadays the most common presentation of patients with GORD, at least those referred to specialised centres for oesophageal investigations. Finally, since it is not easy to justify 24 h pH-impedance monitoring in patients faring well on therapy, we included patients referred for surgery (as preoperative work-up) and patients referred for refractory symptoms who appeared to be adequately controlled after treatment optimisation. We also took the opportunity to include responders in whom the pH-impedance monitoring was performed at baseline of a pharmacological clinical trial. Finally, we performed the analysis in different subgroups of patients. Apart from the whole population, we studied separately the subgroup of patients who reported symptoms during the 24 h pH-impedance monitoring in order to analyse more adequately the role of symptom–reflux association analysis and the subgroup of patients with documented pathological GORD during 24 h pH-impedance monitoring.

The present study is the first outcome study in which the patterns of GOR were determined by 24 h pH-impedance monitoring off PPI. Compared with conventional pH monitoring, impedance provides data on chemical composition (acid, non-acid) as well as the proximal extent of the refluxate within the oesophagus.[17] However, despite the use of this technology,

the multivariate analysis taking into account both clinical and physiological parameters could not identify any reflux pattern associated with PPI failure. As an example, reflux events with high proximal extent have been shown to be associated with persisting symptoms in patients receiving PPIs,[21 22] but the present study failed to demonstrate that patients with a high rate of proximal reflux events were less likely to respond to PPI therapy. Unexpectedly, we could not demonstrate any predictive value of symptom–reflux association analysis with regard to response to PPI therapy, whereas, in the literature, both SI and SAP have been shown to be associated with favourable outcome.[9 14] However, conflicting data have been reported. Broeders *et al* have reported similar outcome after fundoplication among patients with a positive and negative SAP.[26] In a study assessing the performance of these indices compared with the omeprazole test, SI was shown to be unrelated to the results of the test, whereas SAP had a positive predictive value of 79% and a specificity of 73%; SI and SAP were therefore considered by the authors themselves to be 'suboptimal' predictors of response to high-dose omeprazole.[13] Finally, a very recent study showed that SI and SAP may be overinterpreted in patients with refractory GORD, especially when low reflux rates are observed at 24 h pH-alone or pH-impedance monitoring.[27] Taken together, these results raise concerns about the validity and/or usefulness of the indices, at least to predict the response to both medical and surgical therapy. However, we do believe that there is still room for pH-impedance monitoring in patients with refractory GORD on PPI therapy; these indices should be considered as complementary to the 'quantitative' evaluation of reflux, since they can help to identify more patients with symptoms possibly related to GORD.

When the whole population was considered, although the univariate analysis showed that many factors were associated with PPI failure, the multivariate analysis showed that only normal or low BMI, FD and the absence of oesophagitis at endoscopy were significantly and independently associated with PPI failure. Although it is now well established that absence of oesophagitis is associated with poorer response to PPI,[4 5] the relationship between BMI and response to PPIs was initially unexpected, but has been suggested by two recent studies. In a study by Fletcher *et al* in 105 patients with upper gastrointestinal tract (GI) symptoms and normal endoscopy, BMI >25 kg/m^2 and LOS pressure were the only independent factors associated with response to PPI therapy.[28] BMI had a similar predictive value to either 24 h oesophageal pH monitoring or manometry. Unlike the present study, Fletcher *et al* included patients with upper GI symptoms, not only heartburn and regurgitation, but it was observed that predominant symptom and symptom subgroups were unhelpful in predicting the response to PPIs.[28] Heading *et al* performed an open study of 8 weeks pantoprazole 40 mg daily in 1888 patients presenting with symptoms 'considered by the investigating physician to justify a diagnosis of GOR' and also observed poorer treatment responses to be independently associated with lower BMI.[29] Our study is therefore the third to report similar results, whatever the subgroup of patients considered. The mechanisms by which BMI may influence the response to PPIs remain to be elucidated. Hence, high BMI has been clearly associated with the development of reflux symptoms and complications[30 31] through different putative mechanisms such as increased transient LOS relaxations rate,[32] gastro-oesophageal pressure gradient and oesophago–gastric junction disruption—that is, separation of LOS and crural diaphragm leading to hiatal hernia.[33] Therefore high BMI may increase the probability that symptoms are related to GORD, but it is of note that BMI ≤25 kg/m^2 was also independently associated with PPI failure in patients with demonstrated GORD on pH-impedance monitoring.

Several studies have reported the negative impact of functional gastrointestinal disorders on treatment of reflux symptoms.[8 34 35] We have observed that FD and IBS were strongly associated with PPI failure, even in patients with documented abnormal GOR with pH-impedance monitoring. The prevalence of dyspeptic symptoms is high in patients with functional heartburn—that is, with normal oesophageal acid exposure and negative symptom–reflux association analysis.[15] However, in the present study, the role of FD as a predictor of PPI failure was also demonstrated in patients with documented GORD. Although we paid close attention to the nature of the symptoms that persisted during therapy by means of a standardised questionnaire, some patients may have dyspeptic symptoms that may be misinterpreted as reflux symptoms. A recent study that assessed dyspeptic symptoms in patients treated by PPIs did not report any effect of ulcer-like or dysmotility-like symptoms on treatment outcome in patients with upper GI symptoms.[28] The reasons for these discrepancies are not clear, but may be related to different diagnostic criteria for dyspepsia and to the fact that we included patients with typical GOR symptoms as the primary complaint. We also observed that IBS was a predictor of PPI failure in the subgroup of patients with documented abnormal GOR. Similar results have been recently reported by Heading *et al* in patients included on the basis of symptoms only[29]; another study demonstrated that IBS predicted worse quality of life after PPI therapy.[8] The interpretation of this finding is far from easy, since we can reasonably rule out the possibility of symptom misinterpretation. It may be hypothesised that persistent reflux symptoms and IBS symptoms share the same underlying mechanisms (eg, increased visceral perception), since the two conditions often coexist.[6–8 25] Finally, we believe that the presence of functional GI disorders in patients with refractory GORD should be taken into account in future trials with reflux inhibitors.

Our study has several limitations. First, the absence of standardisation of PPI therapy and the use of a recall questionnaire may represent a bias for interpretation of our data. However, regarding the modalities of inclusion in the study together with the use of a standardised questionnaire, the probability of misinterpretation of symptoms is relatively low. Second, we did not assess the level of anxiety in our patients. Anxiety, usually assessed by means of the Hospital Anxiety and Depression Scale, has been shown to be associated with PPI failure.[8] However, conflicting results have been recently reported,[36] and the level of anxiety was normal in a population of patients with refractory GORD included in a pharmacological study.[37] Moreover, the possibility that high anxiety scores may be induced by the persisting reflux symptoms themselves cannot be ruled out.

In conclusion, the results of 24 h pH-impedance monitoring performed off therapy are not predictive of response to PPIs. In patients presenting with typical GORD symptoms as predominant complaint, BMI ≤25 kg/m^2, absence of oesophagitis and functional digestive disorders are the main factors associated with PPI failure through mechanisms that remain to be further elucidated.

Competing interests FZ has served as a speaker, a consultant and an advisory board member for Addex Pharma SA, Xenoport, Movetis, Norgine, Sanofi Aventis, Astrazeneca, Janssen Cilag, Renckitt Benckiser, Abbott, Pfizer, Given Imaging and has received research funding from Nycomed. FM has served as a consultant to Addex Pharma. SBdesV has served as a speaker, a consultant and/or an advisory board

member for Astra Zeneca, Janssen Cilag, Takeda, Danone research, Cephalon, Iprad, Given Imaging, Novartis, Ipsen Beaufour, Nycomed. JPG has served as a speaker, a consultant and an advisory board member for Addex Pharma SA, Xenoport, Movetis, Norgine, AstraZeneca, Janssen Cilag, Renckitt Benckiser, Given Imaging, Mauna Kea Technologies and has received research funding from AstraZeneca, Mauna Kea Technologies, Given Imaging and Janssen-Cilag. KB, MS and MC have no competing interests to disclose.

Contributors FZ, SBdesV, FM and JPG were involved in the study conception, wrote the protocol, analysed and interpreted the data, and drafted the article. KB, MS and MC collected the data and assisted with data interpretation.

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