Esophageal pH-Impedance Monitoring in Patients With Therapy-Resistant Reflux Symptoms: 'On' or 'Off' Proton Pump Inhibitor?

Gerrit J.M. Hemmink, M.D.,[1,2] Albert J. Bredenoord, M.D., Ph.D.,[1] Bas L.A.M. Weusten, M.D., Ph.D.,[1] Jan F. Monkelbaan, M.D.,[3] Robin Timmer, M.D., Ph.D.,[1] and André J.P.M. Smout, M.D., Ph.D.[2]

[1]*Department of Gastroenterology, Sint Antonius Hospital, Nieuwegein, The Netherlands;* [2]*Gastrointestinal Research Center, University Medical Center, Utrecht, The Netherlands; and* [3]*Department of Internal Medicine, Central Military Hospital, Utrecht, The Netherlands*

BACKGROUND: In patients with proton pump inhibitor (PPI)-resistant symptoms, ambulatory 24-h pH-impedance monitoring can be used to assess whether a relationship exists between symptoms and reflux episodes. Until now, it is unclear whether combined pH-impedance monitoring in these patients should be performed on or off PPI.

METHODS: Thirty patients with symptoms of heartburn, chest pain, and/or regurgitation despite PPI twice daily underwent ambulatory 24-h pH-impedance monitoring twice, once on PPI and once after cessation of the PPI for 7 days. The order of the measurements was randomized. Reflux episodes were identified and classified as acid, weakly acidic, or weakly alkaline reflux. In addition, the symptom association probability (SAP) was calculated for each measurement.

RESULTS: The total number of reflux episodes and proximal extent were not affected by PPI therapy. On PPI, there were fewer acid reflux episodes (49 ± 34 off PPI vs 20 ± 25 on PPI) while more weakly acidic reflux episodes were identified (24 ± 17 off PPI vs 48 ± 31 on PPI). Symptom association analysis identified 15 and 11 patients with a positive SAP in the measurement off and on PPI, respectively, the difference in yield of the SAP not being statistically significant. Eight of the 19 patients who had no symptoms or a negative SAP during measurement on PPI had a positive SAP off PPI therapy. In contrast, only 4 patients with a positive SAP on PPI were missed in the measurement off PPI therapy.

CONCLUSIONS: In order to demonstrate or exclude GERD in patients with PPI-resistant symptoms, ambulatory 24-h pH-impedance monitoring should preferably be performed after cessation of PPI therapy because this approach seems to offer the best chance to assess a relationship between symptoms and reflux episodes.

(Am J Gastroenterol 2008;103:2446–2453)

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a very common disorder in the western world; 10–20% of the population experience symptoms of heartburn or regurgitation at least once a week (1, 2). According to the Montreal classification, GERD is a condition that develops when reflux from the stomach into the esophagus causes symptoms and/or mucosal damage (3). Patients who seek medical care are usually treated satisfactorily with proton pump inhibitors (PPI) by general practitioners. However, some patients have persistent symptoms of heartburn, regurgitation, and chest pain despite acid-suppressive therapy. These patients are often referred to a gastroenterologist for further diagnostic workup and treatment.

The most important reason for treatment failure is an erroneous diagnosis of GERD (4). Several functional disorders can be misinterpreted as GERD, and treatment with a PPI is unlikely to resolve the symptoms in these patients.

Second, several studies have shown that weakly acidic reflux episodes can also cause symptoms of heartburn and regurgitation (5–7). Since PPIs do not reduce the number of reflux episodes but only change the acidity, weakly acidic reflux episodes can persist as the cause of symptoms in patients who use PPIs (5, 8).

Another potential cause of treatment failure is insufficient inhibition of gastric acid production by the PPI therapy. This may occur either because of limited effectiveness of the PPI itself (9) or because patients are not compliant to the therapy. Finally, because acid secretion will never be fully inhibited by PPI treatment, a few remaining acidic reflux episodes may be the cause of the patients' symptoms, despite adequate acid-suppressive therapy.

Ambulatory 24-h monitoring of gastroesophageal reflux has been shown to be very helpful in assessing a potential relationship between symptoms and reflux episodes. This used to be done with esophageal pH monitoring after subjects had discontinued their acid-suppressive therapy for several days, because with this technique only acid reflux episodes could be detected. With the recently developed impedance monitoring however, reflux episodes are detected independently of their acidity. This method has been shown to be a sensitive and reproducible method to assess the number and type of reflux episodes and to investigate the relation between symptoms and reflux episodes (7, 10, 11). In patients with PPI-resistant symptoms, it is unclear if 24-h pH-impedance monitoring should be performed on or off PPI therapy. Therefore, the aim of our study was to compare the yield of 24-h pH-impedance monitoring off and on PPI therapy in GERD patients with PPI-resistant symptoms.

METHODS

Subjects

For this multicenter randomized crossover study, patients with typical reflux symptoms (heartburn, regurgitation, and/or chest pain) despite PPI therapy twice daily (b.i.d.) were included. Patients with a history of esophageal or gastric surgery were excluded. All patients were recruited from the population of patients at the St. Antonius Hospital Nieuwegein, the Universital Medical Center Utrecht, and the Central Military Hospital in Utrecht, The Netherlands. Written informed consent was obtained from all subjects before the start of the study and the protocol was approved by the local medical ethical committees.

Study Protocol

Prior to the ambulatory measurements, all patients underwent upper endoscopy on PPI therapy. Combined ambulatory 24-h pH-impedance monitoring was performed twice on two separate occasions with an interval varying between 1 and 4 wk. In a randomized order, one measurement was performed after cessation of PPI for 7 days, while the other measurement was performed on double dose PPI therapy (b.i.d.). Before the first measurement, the lower esophageal sphincter (LES) was located by stationary manometry in order to position the pH-impedance catheter correctly.

Esophageal Impedance and pH Monitoring

For the ambulatory measurements, a combined pH-impedance catheter was used (VersaFlex, Alpine Biomed, Fountain Valley, CA). This catheter contains a single antimony pH electrode and 8 ring electrodes for impedance measurements, which enable recording from 6 segments, each segment 2 cm long.

After detection of the LES by manometry, the combined pH-impedance catheter was placed with the antimony pH electrode 5 cm above the upper margin of the LES. Impedance recording segments were located at 2–4 cm, 4–6 cm, 6–8 cm, 8–10 cm, 14–16 cm, and 16–18 cm above the upper margin of the LES.

Impedance and pH data were stored in a digital datalogger (Ohmega, MMS, Enschede, The Netherlands) using a sample frequency of 50 Hz and 1 Hz, respectively.

During both measurements, patients were instructed to have three meals and four beverages at fixed times. The patients kept a diary in which periods of ingestion and periods spent in recumbent position were noted. Furthermore, the patients were instructed to press the event marker button on the digital datalogger whenever they experienced a symptom and to describe the nature and onset of their symptoms in the diary. To obtain a representative measurement with symptoms, patients were encouraged to maintain their normal daily activities.

Data Analysis

Analyses of the 24-h recordings were carried out after the second measurement was completed and all recordings were analyzed manually.

Reflux episodes were defined as a fall in impedance of ≥50% of baseline impedance that moved in retrograde direction in the two distal impedance sites. Reflux episodes were considered to have reached the proximal esophagus when the impedance fall reached the two most proximal recording segments located at 14–18 cm above the LES. Reflux episodes were classified as mid-esophageal reflux episodes if they reached the middle recording segments (6–10 cm above the LES) and as distal reflux episodes when they reached only the two distal recording segments (2–6 cm above the LES).

Reflux episodes were classified as acid when the pH dropped below 4, and as weakly acidic when pH nadir was between 4 and 7. Weakly alkaline reflux was defined as a reflux episode during which the pH did not drop below 7 (12). Periods of meal consumption were excluded from the analysis. Acid exposure time was calculated as the percentage of time with pH below 4. Excessive acid exposure was defined as the percentage of time with pH<4 >6.0% off PPI therapy (13) while on therapy an acid exposure time of >1.6% was defined as indicative of inadequate acid suppression (14).

Symptom Analysis

Symptom-reflux association analysis was carried out to investigate the relationship between the occurrence of reflux episodes and symptoms. Only typical reflux symptoms (heartburn, chest pain, and regurgitation) were used for further analysis (15). Reflux episodes were considered symptomatic when a symptom episode occurred in the 2-min time window preceding the reflux episode (16). The symptom index (SI) and the symptom association probability (SAP) (17) were calculated. When the SAP was ≥95%, the patients' symptoms reflux episodes were considered to be related to gastroesophageal reflux.

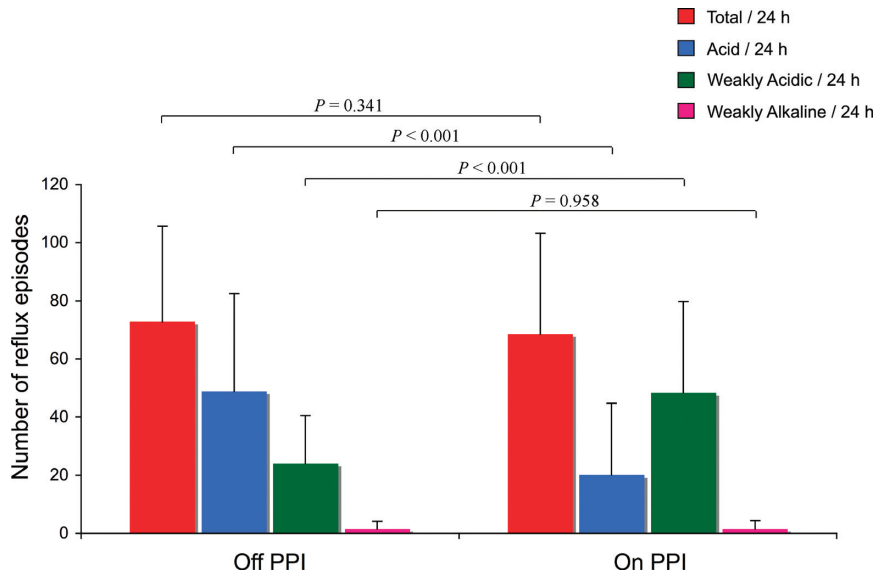**Figure 1.** Total numbers and numbers of acid, weakly acidic and weakly alkaline reflux episodes are shown, off and on PPI therapy (mean + SD).

Statistical Analysis

The parametric data are presented as mean ± standard deviation and comparisons were performed using the paired Student's *t*-test. The nonparametric data are presented as median (interquartile range) and were compared using the Wilcoxon signed rank test. The McNemar test was used to compare the results of the symptom association analysis between both measurements. A *P* value <0.05 was considered to be statistically significant.

RESULTS

Patients

Thirty-seven patients were enrolled in the study. Three patients were excluded because of failure of the hardware, and 4 patients were not willing to undergo the second measure-

ment. Thirty patients (mean age 46.5 yr, range 19.1–71.8 yr, 20 men) underwent both measurements successfully.

All 30 patients underwent upper endoscopy on PPI therapy prior to the 24-h pH-impedance measurements. According to the Los Angeles classification, grade C esophagitis was present in two patients and grade B esophagitis in one patient. Four patients had a hiatal hernia larger than 3 cm.

Reflux Parameters

As expected, the total number of reflux episodes was not influenced by PPI therapy (73 ± 33 off PPI *vs* 69 ± 35 on PPI, [*P* = 0.341]) (Fig. 1). In addition, the percentage of reflux episodes reaching the proximal (*P* = 0.271), mid- (*P* = 0.824), or distal esophagus (*P* = 0.241) did not change significantly between the two measurements (Fig. 2).
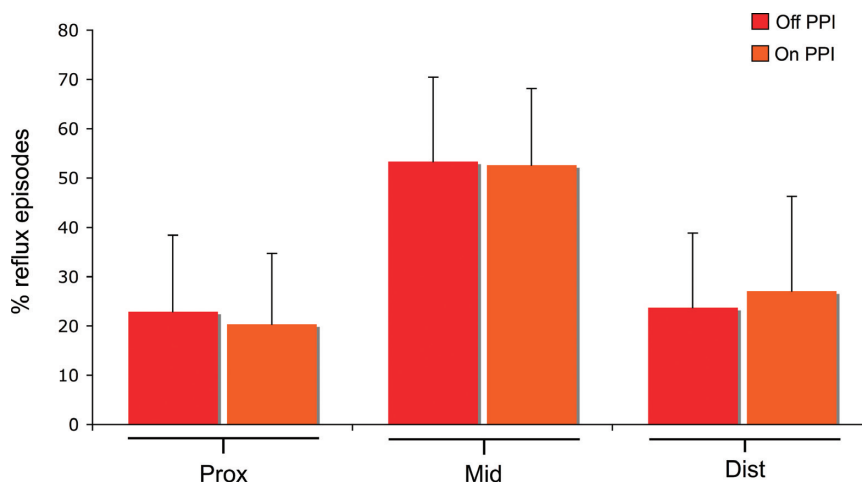

Figure 2. Percentage of reflux episodes reaching the proximal, middle, and distal esophagus off and on PPI therapy.

Table 1. Median (Interquartile Range) Acid Exposure Time (% of Time With pH < 4) off and on PPI Therapy in Total and in Upright and Supine Position

Acid Exposure Time	Off PPI	On PPI	P Value
Total (%)	5.0 (2.0–14.2)	1.1 (0.2–6.3)	< 0.01
Upright (%)	7.5 (2.6–13.8)	1.5 (0.3–8.9)	< 0.01
Supine (%)	0.5 (0.0–6.8)	0.0 (0.0–1.3)	0.12

During the measurement on PPI, the number of acid reflux episodes was lower (49 ± 34 off PPI *vs* 20 ± 25 on PPI [$P < 0.001$]) while more weakly acidic reflux episodes were found (24 ± 17 off PPI *vs* 48 ± 31 on PPI [$P < 0.001$]) in comparison with the measurement off PPI. Compared to the number of acid and weakly acidic reflux episodes, the number of weakly alkaline reflux episodes was very low (2 ± 3 off PPI *vs* 2 ± 3 on PPI) and was not affected by the PPI therapy ($P = 0.958$). As expected, the percentage of time with pH below 4 was less during PPI therapy (off PPI 5.0% [2.0–14.2%], on PPI 1.1% [0.2–6.3%], $P = 0.007$) (Table 1).

Symptom Association Analysis

The individual results of the symptom association analysis are shown in Table 2 and summarized in Table 3. During the measurement off PPI, 2 patients reported no reflux symptoms. In the remaining 28 symptomatic patients, symptom analysis was performed and this resulted in the identification of 13 patients with a negative SAP and 15 patients with a positive SAP. Nineteen patients had a positive SI and 9 patients had a negative SI.

During the measurement on PPI 7 patients were asymptomatic. In the remaining 23 patients, a negative SAP was found in 12 patients and a positive SAP in 11 patients (Fig. 3). Twelve patients had a positive SI and 11 patients had a negative SI.

The result of symptom association analysis was concordant for both measurements in only 15 patients. Seven patients had a negative SAP and 7 patients had a positive SAP in both measurements. One patient was asymptomatic during both measurements (Table 3).

In the other 15 patients, the results of the two measurements were discordant. Seven patients were asymptomatic during one of the measurements (1 patient off PPI and 6 patients on PPI); as a result no SAP could be calculated. In these patients, the other measurement identified 4 patients with a positive and 3 patients with a negative SAP. In the remaining 8 patients, a different SAP was calculated for both

Table 2. Individual Results of Acid Exposure Times and Symptom Association Analysis off and on PPI

	AET off PPI (%)	AET on PPI (%)	SI off PPI (%)	SI on PPI (%)	SAP off SPPI (%)	SAP on PPI (%)
1	6.3	0.0	+	No Sx	+	No Sx
2	2.2	0.4	+	No Sx	−	No Sx
3	7.9	11.4	+	+	+	+
4	0.1	0.2	0	−	0	−
5	1.3	0.1	0	−	0	−
6	33.3	1.2	+	+	+	+
7	3.3	10.3	−	0	−	0
8	1.8	4.1	0	+	0	+
9	5.1	0.7	No Sx	+	No Sx	+
10	11.0	0.1	+	+	+	+
11	5.0	0.3	0	0	0	0
12	5.4	1.4	+	No Sx	−	No Sx
13	2.6	1.4	+	0	−	0
14	10.2	0.2	+	0	+	0
15	1.6	1.1	+	No Sx	−	No Sx
16	4.9	1.3	+	+	+	+
17	15.1	11.7	+	+	+	+
18	2.0	9.2	−	+	−	+
19	2.9	1.1	+	0	+	0
20	21.2	13.7	+	No Sx	+	No Sx
21	18.2	30.6	+	0	−	0
22	0.3	0.1	No Sx	No Sx	No Sx	No Sx
23	4.2	5.1	+	+	+	+
24	0.0	0.0	−	0	+	0
25	21.0	0.2	+	0	+	0
26	24.7	10.7	+	+	+	+
27	3.3	0.0	0	+	0	+
28	1.1	0.2	−	−	−	−
29	13.9	0.8	+	No Sx	+	No Sx
30	17.3	5.3	+	+	+	−

AET: acid exposure time (excessive acid exposure time is defined as the percentage of time with pH<4 >6.0% [13] or >1.6% [14] off or on PPI therapy, respectively). SI: symptom index (+: ≥ 50%, −: < 50%; 0: no symptoms related to reflux; No Sx: no symptoms) SAP: symptom association probability (+: ≥ 95%, −: < 95%; 0: no symptoms related to reflux; No Sx: no symptoms).

Table 3. Concordance of the Results of Symptom Association Analysis off and on PPI Therapy (Number of Patients)

		On PPI			
		No Sx	SAP–	SAP+	
Off PPI	No Sx	1	0	1	2
	SAP–	3	7	3	13
	SAP+	3	5	7	15
		7	12	11	30

No Sx: Asymptomatic during 24-h monitoring; SAP–: negative symptom association probability; SAP+: positive symptom association probability.

measurements: 5 patients had a positive SAP in the measurement off PPI and a negative SAP in the measurement on PPI and 3 patients had a positive SAP in the measurement on PPI and a negative SAP off PPI. Of these 3 patients, 1 patient had a hiatus hernia and esophagitis (grade C). This patient had an excessive acid exposure time only during the measurement on PPI. The other patients had normal upper endoscopy. One patient had normal esophageal acid exposure during both measurements and the other patient had an excessive acid exposure only during the measurement on PPI.

Eight patients without a positive SAP on PPI (3 asymptomatic and 5 patients with a negative SAP) had a positive SAP in the measurement off PPI. In contrast, during the measurement off PPI, 4 patients who had a positive SAP on PPI were missed and did not have a good relation between symptoms and reflux episodes (3 patients) or were asymptomatic (1 patient) during this measurement. The differences in yield of the SAP between both measurements (Table 3) were not statistically significant ($P = 0.118$).

In order to investigate a potential sequence effect, the results of the first measurement were compared with the second measurement, regardless of PPI use. In the first measurement, 16 out of 34 (47%) patients had a positive SAP and in the second measurement 13 out of 30 (43%) patients had a positive SAP, indicating that the results are not likely to be influenced by a sequence effect.

Three out of the four patients who were not willing to undergo the second measurement had a positive SAP, and were all measured after cessation of PPI therapy. The other patient, who was measured on PPI, had a negative SAP.

When the pH recordings were analyzed independently of the impedance tracings, symptom association analysis resulted in a positive SAP in 12 patients during one or both measurements. Eleven and 7 patients had a positive SAP for acid reflux in the measurement off and on PPI, respectively. Six patients had a positive SAP for acid reflux during both measurements. Thus pH-impedance monitoring had a higher yield than pH monitoring alone since it allowed identification of 4 additional patients with a positive SAP off PPI and 4 additional patients with a positive SAP on PPI therapy.

In the measurements off PPI, excessive acid exposure (defined as percentage of time with pH<4 greater than 6.0%) was found in 12 patients. In the measurement on PPI, 10 patients had excessive acid exposure (defined as percentage of time with pH<4 greater than 1.6) (Table 4). Six patients had an excessive acid exposure during both measurements.

Of the 18 patients with a normal acid exposure off PPI, 2 patients had a positive SAP identified on pH monitoring alone. The remaining 16 patients were asymptomatic (N = 2) or had a negative SAP (N = 14). Of these 16 patients, 4 patients were asymptomatic, 8 had a negative SAP, and 4 patients had a positive SAP during the combined pH-impedance measurement on PPI.

The number of symptoms and number of symptoms related to reflux was significantly lower during the measurement on PPI (3 [1–6] and 1 [0–3], respectively) compared to the measurement off PPI (5 [2–10] [$P = 0.004$] and 2 [1–6] [$P = 0.010$], respectively).

During PPI therapy, the number of heartburn episodes related to reflux decreased significantly (1 [0–4] off PPI *vs* 0 [0–1] on PPI, $P = 0.006$) while the numbers of chest pain episodes and regurgitation were not significantly different ($P = 0.755$ and $P = 0.507$, respectively). In the measurement on PPI, a high proportion (71.9%) of heartburn episodes
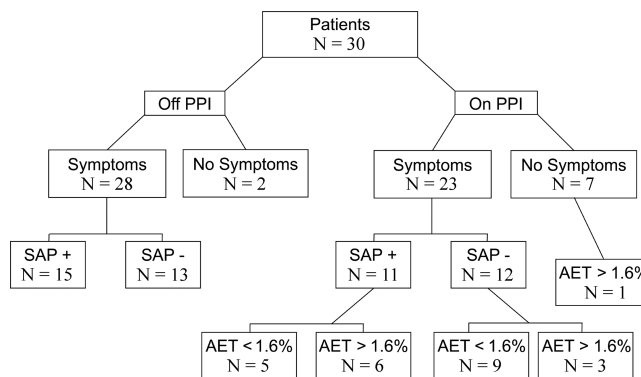

Figure 3. Results of symptom association analysis off and on PPI therapy and relationships with adequately (% of time with pH<4 <1.6%) and inadequately suppressed acid exposure (% of time with pH<4 ≥1.6%) during PPI therapy. SAP: symptom association probability; SAP+: SAP≥95%; SAP–: SAP<95%; AET: acid exposure time.

Table 4. Number of Patients With Normal and Excessive Acid Exposure off and on PPI Therapy

Acid Exposure	30 Patients	
	Off PPI	On PPI
Normal	18	20
No Sx	2	6
SAP−	12	9
SAP+	4	5
Excessive	12	10
No Sx	0	1
SAP −	1	3
SAP +	11	6

Excessive acid exposure is defined as percentage of time with pH<4 more than 6.0% (13) and 1.6% (14) off and on PPI, respectively. No Sx: asymptomatic; SAP−: negative symptom association probability; SAP+: positive symptom association probability.

related to reflux was still preceded by an acid reflux episode (Fig. 4).

DISCUSSION

This is the first study in which ambulatory esophageal 24-h pH-impedance monitoring both on and off PPI therapy was carried out in one and the same group of patients with PPI-refractory reflux symptoms. The specific aim of our study was to determine which of the two approaches is optimal in the workup of these patients, measurement after temporary interruption of PPI therapy, or measurement while PPI treatment is continued. The former approach allows one to measure baseline esophageal acid exposure, a traditional and robust measure of the severity of gastroesophageal reflux. The latter approach offers the possibility to assess the adequacy of PPI treatment in terms of remaining esophageal acid exposure. Both approaches allow assessment of the temporal association between symptom episodes and reflux events.

In our opinion, the first and most important question that needs to be addressed in patients with PPI-refractory reflux symptoms is whether or not their symptoms are brought about by reflux. Therefore, in the interpretation of the results of our study we considered the yield of symptom association analysis as the primary study outcome. Since the SAP takes both the numbers of reflux events as the number of symptoms into account, we relied primarily on the SAP to distinguish between patients with a good relation between symptoms and reflux episodes and those without.

We showed that performing both measurements has the highest yield as far as the identification of patients with a positive SAP is concerned. Of course, this is not the most desirable approach in the majority of patients.

Our observation that 50% of the patients had a positive SAP off PPI and 37% on PPI therapy is in accordance with previously published data. In a study with 24-h pH-impedance monitoring in 168 patients on PPI, 39% of the patients had a positive SAP (18). Zerbib *et al.* (19) performed a symptom association analysis off and on PPI therapy in two separate patient groups: 79 patients were studied off PPI and 71 patients on PPI therapy. Fifty-two percent of the patients off PPI and 31% of the patients on PPI therapy had a positive SAP, which suggests a higher yield of the ambulatory reflux monitoring after cessation of PPIs.

A higher proportion of our patients was asymptomatic during the measurement on PPI (6.7% off and 23.3% on PPI therapy). This, again, is in agreement with findings made by Zerbib *et al.* (19). Obviously, the absence of symptoms during the measurement on PPI led to a decreased yield of the symptom association analysis. Two possible explanations for the lack of symptoms during the measurement on PPI therapy can be proposed. First, patients could be more compliant to the PPI therapy during the study. Second, the patients' recollection of symptoms occurring despite PPI may not be correct. We chose not to exclude the patients who were asymptomatic in one of the two measurements for the analysis, because this reflects the situation in daily practice best.

In addition, almost half of the symptomatic patients with a negative SAP on PPI had a positive SAP in the
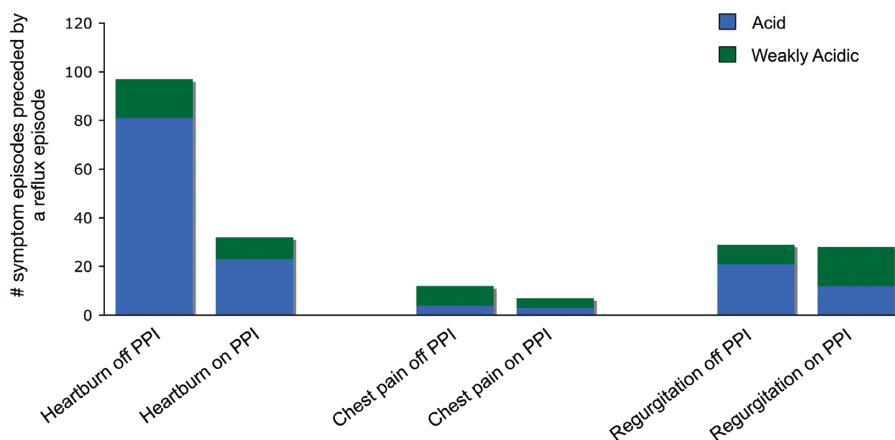

Figure 4. Number of symptom episodes (heartburn, chest pain, regurgitation) preceded by acid and weakly acidic reflux episodes off and on PPI therapy.

measurement off PPI therapy. In contrast, only 4 of the 15 patients without a positive SAP off PPI had a positive SAP during PPI therapy. The higher proportion of patients with a positive SAP off PPI therapy is largely due to the lower incidence of symptom episodes during PPI therapy, since the number of reflux episodes and the proportion of symptoms related to reflux were the same in both measurements.

Among the symptom episodes scored, episodes of heartburn decreased during PPI therapy, while the frequencies of regurgitation and chest pain were not influenced by the PPI therapy. This is in accordance with the observation that heartburn is more commonly provoked by acid reflux (5). Regurgitation and chest pain appear to be less acid-dependent.

Endoscopy did not contribute to the diagnostic workup of GERD as it revealed esophagitis in only 3 patients. A negative endoscopy has low diagnostic value for GERD, especially when performed on PPI therapy.

The total number of identified reflux episodes was comparable with previous data from our group (20–22) but was high compared to findings of other groups (18, 19). An explanation may be that our patients are explicitly encouraged to do their normal daily activities and not to avoid food and beverages that elicit symptoms.

An argument in favor of a measurement off PPI therapy is the possibility to evaluate the severity of naïve esophageal acid exposure, which is a parameter that predicts the response to antireflux surgery (23). This parameter can be useful when antireflux surgery is considered.

Ten patients had an acid exposure during PPI therapy of more than 1.6% (14), indicating that acid secretion was not adequately inhibited. Some of these patients may have an increased metabolism of the PPI by the cytochrome systems in the liver (9), others may not have been not fully compliant to the therapy. Only 6 of the 11 patients with a positive SAP on PPI therapy had an insufficiently suppressed acid exposure. Five patients had a positive SAP despite adequate acid-suppressive therapy.

In agreement with previous studies, this study confirms the increased yield of combined pH-impedance monitoring compared to classic pH monitoring (19, 20). In 4 of the 15 patients the addition of impedance monitoring was necessary to obtain a positive SAP off PPI therapy. In the measurement on PPI therapy the addition of impedance monitoring to pH monitoring increased the number of patients with a positive SAP from 7 to 11. In 4 of the 16 patients without a positive SAP and with a normal acid exposure time during pH monitoring off PPI, a positive SAP was found during the combined pH-impedance measurement on PPI.

It should be stressed that observed differences in yield of symptom association analysis between both measurements were not statistically significant, likely due to the relatively small sample size. The lack of concordance between both measurements is indicative of the fact that GERD varies day-by-day. Since the measurement off PPI resulted in the highest yield of the symptom association analysis, we consider this approach the most desirable. In patients in whom the reflux-ogenic origin of the symptoms has been established before, and in whom there is doubt about the effectiveness of the PPI therapy, 24-h pH-impedance monitoring on PPI therapy can provide information about the degree of acid suppression that is obtained.

In conclusion, no statistically significant difference in yield of symptom association analysis between both approaches was found. In our opinion, to exclude or confirm GERD as the cause of symptoms in patients with PPI-resistant symptoms, ambulatory 24-h pH-impedance monitoring should preferably be performed after cessation of PPI therapy. This approach offers the best chance to assess the relationship between symptoms and reflux events in these patients. When reflux has been identified as the likely cause of the symptoms, measurement of remaining esophageal acid exposure during PPI treatment becomes more meaningful.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Most patients with symptoms of gastroesophageal reflux disease (GERD) respond satisfactorily to proton pump inhibitor (PPI) therapy.
- The most important reason for treatment failure is an erroneous diagnosis of GERD.
- Combined pH-impedance monitoring has additional yield in identifying GERD patients compared to pH monitoring alone and can be performed on and off PPI therapy.

What Is New Here

- PPI therapy does not influence the total number or proximal extent of reflux episodes.
- To exclude or diagnose GERD in patients with PPI-resistant symptoms, 24-h pH-impedance monitoring should preferably be performed off PPI therapy.

REFERENCES

1. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut 2005;54:710–7.
2. Locke GRr, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: A population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112:1448–56.
3. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. Am J Gastroenterol 2006;101:1900–20.

4. Smout AJ. The patient with GORD and chronically recurrent problems. Best Pract Res Clin Gastroenterol 2007;21:365–78.
5. Vela MF, Camacho-Lobato L, Srinivasan R, et al. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: Effect of omeprazole. Gastroenterology 2001;120:1599–606.
6. Bredenoord AJ, Weusten BL, Curvers WL, et al. Determinants of perception of heartburn and regurgitation. Gut 2006;55:313–8.
7. Sifrim D, Holloway R, Silny J, et al. Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology 2001;120:1588–98.
8. Tamhankar AP, Peters JH, Portale G, et al. Omeprazole does not reduce gastroesophageal reflux: New insights using multichannel intraluminal impedance technology. J Gastrointest Surg 2004;8:890–7; discussion 897–8.
9. Furuta T, Shirai N, Watanabe F, et al. Effect of cytochrome P4502C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. Clin Pharmacol Ther 2002;72:453–60.
10. Bredenoord AJ, Weusten BL, Timmer R, et al. Reproducibility of multichannel intraluminal electrical impedance monitoring of gastroesophageal reflux. Am J Gastroenterol 2005;100:265–9.
11. Aanen MC, Bredenoord AJ, Smout AJ. Reproducibility of symptom-reflux association analysis with 24-hour esophageal impedance-pH recordings. Gastroenterology 2007;132:A472.
12. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: Review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024–31.
13. Smout AJ, Breedijk M, Van Der Zouw C, et al. Physiological gastroesophageal reflux and esophageal motor activity studied with a new system for 24-hour recording and automated analysis. Dig Dis Sci 1989;34:372–8.
14. Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: Effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol 1996;91:1532–8.
15. Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet 1990;335:205–8.
16. Lam HG, Breumelhof R, Roelofs JM, et al. What is the optimal time window in symptom analysis of 24-hour esophageal pressure and pH data? Dig Dis Sci 1994;39:402–9.
17. Weusten BL, Roelofs JM, Akkermans LM, et al. The symptom-association probability: An improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994;107:1741–5.
18. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: A multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398–402.
19. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: A study in patients off and on therapy. Am J Gastroenterol 2006;101:1956–63.
20. Bredenoord AJ, Weusten BL, Timmer R, et al. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. Am J Gastroenterol 2006;101:453–9.
21. Bredenoord AJ, Weusten BL, Timmer R, et al. Characteristics of gastroesophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. Am J Gastroenterol 2006;101:2470–5.
22. Conchillo JM, Schwartz MP, Selimah M, et al. Acid and non-acid reflux patterns in patients with erosive esophagitis (EE) and non-erosive reflux disease (NERD): A study using intraluminal impedance monitoring. Dig Dis Sci 2008;53:1506–12.
23. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg 1999;3:292–300.

CONFLICT OF INTEREST