

ORIGINAL CONTRIBUTIONS

Esophageal pH-Impedance Monitoring and Symptom Analysis in GERD: A Study in Patients off and on Therapy

Frank Zerbib, M.D., Ph.D.,¹ Sabine Roman, M.D.,² Alain Ropert, M.D., Ph.D.,³ Stanislas Bruley des Varannes, M.D., Ph.D.,⁴ Philippe Poudroux, M.D., Ph.D.,⁵ Ulriikka Chaput, M.D.,⁶ François Mion, M.D., Ph.D.,² Eric Vérin, M.D., Ph.D.,⁶ Jean-Paul Galmiche, M.D., F.R.C.P.,⁴ and Daniel Sifrim M.D., Ph.D.⁷

¹Gastroenterology Department, Saint André Hospital, Bordeaux, France; ²Digestive Physiology Department, Edouard Herriot Hospital, Lyon, France; ³Digestive Physiology Department, Pontchaillou Hospital, Rennes, France; ⁴Digestive Diseases Institute, CIC-INSERM, Hôtel Dieu, Nantes, France; ⁵Gastroenterology Department, Caremeau Hospital, Nîmes, France; ⁶Digestive Physiology Department, Charles Nicolle Hospital, Rouen, France; and ⁷Center for Gastroenterological Research, Catholic University of Leuven, Leuven, Belgium

INTRODUCTION: Combined esophageal pH-impedance monitoring allows detection of nearly all gastroesophageal reflux episodes, acid as well as nonacid. However, the role of nonacid reflux in the pathogenesis of symptoms is poorly known. The aim of this study was to evaluate the diagnostic yield of this technique in patients with suspected reflux symptoms while on or off PPI therapy.

PATIENTS AND METHODS: The recordings of 150 patients recruited at seven academic centers with symptoms possibly related to gastroesophageal reflux were analyzed. Reflux events were detected visually using impedance (Sandhill, CO) and then characterized by pHmetry as acid or nonacid reflux. The temporal relationship between symptoms and reflux episodes was analyzed: a symptom association probability (SAP) $\geq 95\%$ was considered indicative of a positive association.

RESULTS: One hundred fifty patients were included, 102 women (mean age 52 ± 14 yr, range 16–84). Among the 79 patients off PPI, five did not report any symptom during the recording period. A positive SAP was found in 41 of the 74 symptomatic patients (55.4%), including acid reflux in 23 (31.1%), nonacid reflux in three (4.1%), and acid and nonacid in 15 (20.3%). In the group of patients on PPI (N = 71, 46 women, mean age 51 ± 15 yr), 11 were asymptomatic during the study, SAP was positive in 22 of the 60 symptomatic patients (36.7%), including acid reflux in three (5.0%), nonacid reflux in 10 (16.7%), and acid and nonacid in nine (15.0%). The symptoms most frequently associated with nonacid reflux were regurgitation and cough.

CONCLUSION: Adding impedance to pH monitoring improves the diagnostic yield and allows better symptom analysis than pHmetry alone, mainly in patients on PPI therapy. The impact of this improved diagnostic value on gastroesophageal reflux disease management remains to be investigated by outcome studies.

(Am J Gastroenterol 2006;101:1956–1963)

INTRODUCTION

The role of the acid component of the refluxate in the pathophysiology of gastroesophageal reflux disease (GERD) has been confirmed by experimental and esophageal pH-monitoring studies (1). Considering symptoms and mucosal damage, the pivotal role of acid is reinforced by the remarkable efficacy of acid-suppressive therapies for mucosal healing and symptom relief (2). However, some patients with GERD are refractory to adequate acid-suppressive therapy (3), suggesting that other factors either in the esophagus or in the refluxate may play an additional role in the pathogenesis of GERD.

Esophageal pH monitoring does not detect all gastroesophageal reflux events, particularly when little or no acid is present in the refluxate. Multichannel intraluminal impedance monitoring is a recently developed technique that allows detection of virtually all reflux episodes, liquid, gas, or mixed. When combined with pH monitoring, it allows the characterization of reflux episodes as acid or nonacid and has been considered by a panel of experts in the field of GERD as the best tool to detect and characterize gastroesophageal reflux (4). Combined pH-impedance recording enables to detect nonacid reflux and analyze its association with symptoms in ambulatory physiological conditions. Recent ambulatory studies in healthy subjects have shown that nonacid reflux

represents 40–60% of all gastroesophageal reflux detected by impedance (4–6). The first data available in GERD patients have suggested that nonacid reflux may be responsible for symptoms such as chronic cough (7) and regurgitation in patients on proton pump inhibitors (PPIs) (8). Some recent data suggest that nonacid reflux may be responsible for persistent symptoms in patients on PPIs (9), but the relevance of nonacid reflux and, therefore, the usefulness of pH-impedance recordings in the clinical setting are still unclear.

A consortium was created in 2003 in France and Belgium that aimed to homogenize the use and analysis of pH-impedance monitoring thanks to several meetings and training sessions. Our collaborative group recently published its reference values (6). During the same period, a quite large cohort of patients referred to our centers was investigated either for (a) diagnostic purpose, patients being off therapy, or (b) partial or complete refractoriness to PPI. We report here our experience of 150 investigations to assess the prevalence of nonacid reflux and its association with symptoms in patients with suspected GERD, in order to evaluate the clinical usefulness of pH-impedance recordings.

PATIENTS AND METHODS

Patients

Between November 2003 and October 2005, patients with symptoms suggestive or potentially related to GERD were prospectively included in seven centers. Exclusion criteria were: history of thoracic, esophageal, or gastric surgery, primary or secondary severe esophageal motility disorders (*e.g.*, achalasia, scleroderma). The patients were divided into two groups: group I consisted of patients studied without any antisecretory therapy (“off therapy”) for at least 10 days while in group II were included patients on PPI. In group II, patients could have either previously documented GERD by endoscopy and/or pH study (*i.e.*, symptoms refractory to PPI) or persistent symptoms on PPI prescribed empirically for at least 2 wk before the pH-impedance study. All patients had either a double dose of PPI, *i.e.*, twice-daily omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, pantoprazole 40 mg, esomeprazole 40 mg, or a single dose of esomeprazole (40 mg o.d.).

Impedance-pH Equipment

Esophageal impedance-pH monitoring was performed using a Sleuth[®] Multi-channel Intraluminal Impedance ambulatory system (Sandhill Scientific, Inc.; Highland Ranch, CO). 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.

Study Protocol

The studies were performed on an outpatient basis after an overnight fast. Before the start of the recordings, the pH recorder was calibrated using pH 4.0 and 7.0 buffer solutions.

After LOS location by esophageal manometry, the impedance-pH catheter was passed transnasally under topical anesthesia and positioned in the esophageal 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, 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 bedtime. Event markers on the data-logger recorded symptoms, meal times, and posture changes.

Data Analysis

The data stored on the CompactFlash card were downloaded onto a personal computer and visually analyzed using assistance of dedicated software (Bioview Analysis[®], version 5.0.9, Sandhill Scientific, Inc.). Prior to the study, investigators from each center participated in a series of workshops aimed at training on visual characterization of gastroesophageal reflux by esophageal impedance-pH. These training sessions were organized in order to reduce interobserver variability and improve the interpretation of impedance-pH tracings.

Analysis included identification, enumeration, and characterization of individual reflux events, measure of clearance times (bolus and pH clearance), and finally of esophageal exposure to volume and acid.

DEFINITIONS OF REFLUX EPISODES. Liquid reflux was defined as a retrograde 50% drop 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 lasting at least 3 s was taken into account. Gas reflux was defined as a rapid (3 k Ω /s) increase in impedance >5,000 Ω , occurring simultaneously at least in two esophageal 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 considered separately and were not characterized by pH.

Reflux episodes were characterized by pHmetry as acid, weakly acidic, or weakly alkaline according to a recently published consensus report on detection and definitions of gastroesophageal reflux (4): (i) *Acid reflux*: refluxed gastric juice with a pH less than 4, which can either reduce the pH of the esophagus to below 4 or occur when esophageal pH is already below 4; (ii) *Weakly acidic reflux*: reflux events that

result in an esophageal pH between 4 and 6.5; (iii) *Weakly alkaline reflux*: reflux episodes during which nadir esophageal pH does not drop below 6.5. A slight modification of the Porto Consensus definitions was used to differentiate weakly acidic from weakly alkaline reflux, considering pH 6.5 instead of pH 7 as a limit between them. For symptom analysis, the distinction between weakly acidic reflux and weakly alkaline reflux is not possible. Therefore, "nonacid reflux" refers to weakly acidic and weakly alkaline reflux, *i.e.*, all reflux episodes during which nadir esophageal pH does not drop below 4.

GASTROESOPHAGEAL REFLUX PARAMETERS. All reflux events were analyzed during both upright and supine positions and the following parameters were obtained from the impedance and pH recordings: number of reflux episodes, bolus exposure (reflux time [min] and reflux percent time), proximal extent (reflux reaching 15-cm impedance site), and median bolus clearance time. Meals were excluded for the analysis.

Total 24-h esophageal acid exposure (%) was defined as the total time at pH below 4 divided by the time of monitoring.

For comparisons, normal values were obtained from a recent study by the same collaborative group (6) in 72 healthy subjects studied in ambulatory conditions with nonstandardized meals. For these comparisons only, nonacid reflux events were divided in weakly acidic and weakly alkaline reflux. The 95th percentile values obtained in this series were considered to be the upper limit of normal values.

SYMPTOM-REFLUX ASSOCIATION ANALYSIS. A per individual analysis was performed using both symptom index (SI) and symptom association probability (SAP). The software used allowed separation of symptoms into those associated with acid reflux and nonacid reflux (including weakly acidic and weakly alkaline reflux as a whole). Separate analysis was performed for each individual symptom if patients recorded different types of symptoms.

SAP was calculated for acid and nonacid reflux using dedicated software (gift from Dr. Radu Tutuian, University Hospital, Zurich, Switzerland) by dividing 24-h pH data into consecutive 2-min segments. For each of these 2-min segments, it was determined whether reflux and/or symptoms occurred. A 2 × 2 contingency table was then constructed in which the numbers of 2-min segments with and without symptoms and with and without reflux were tabulated. A χ^2 test was used to calculate the probability (p) that the observed distribution could have been brought about by chance. SAP was calculated as $(1 - p) \times 100\%$ and was considered to be positive when $\geq 95\%$ was positive (10).

Bioview Analysis[®] software was used for calculation of SI. According to the setting of this software, symptoms were considered as being related to reflux if they occurred within a 5-min time window after the onset of the reflux episode. SI was defined as the number of symptoms associated with

reflux divided by the total number of symptoms. A positive SI (SI+) was declared if $\geq 50\%$ (*i.e.*, at least half of symptoms associated with reflux) (11).

Statistical Analysis

Because data were not normally distributed they were expressed as median and percentile values (25th, 75th, 95th percentile).

RESULTS

Group I: Patients off Therapy

This group consisted of 79 patients, 56 women (70.9%), mean age 52 ± 13 , range 18–82 yr. During the monitoring period, 74 patients (93.7%) reported at least one type of symptom, 50 (63.2%) reported two different types of symptoms, and 26 (32.9%) reported three different types of symptoms.

NUMBER AND CHARACTERISTICS OF REFLUX EVENTS. The numbers of different types of gastroesophageal reflux events detected during the pH-impedance studies are indicated in Figure 1. The total number of reflux (median value 45) as well as median numbers of acid (22), weakly acidic (8), and weakly alkaline reflux (1) were very similar to those observed in normals (respectively, 44, 22, 11, and 3). The numbers of patients with abnormal values are indicated in Table 1. Respectively, 16 (20.2%) and 15 (18.9%) subjects had a total number of reflux and acid reflux above normal values. Esophageal exposure to volume (bolus exposure) and to acid were above normal values in, respectively, 20 (25.3%) and 17 (21.5%) subjects. However, the number of subjects with abnormal numbers of weakly acidic and weakly alkaline reflux was much lower ($N = 5$, 6.3%).

SYMPTOM-REFLUX ASSOCIATION. Seventy-four subjects reported symptoms during the pH-impedance study. Forty-one of the symptomatic subjects (55.4%) had positive SAP. The symptom association with acid and nonacid reflux is shown in Figure 2. As shown in Figure 3, pH-impedance monitoring allowed establishing a temporal association between reflux and symptoms in 4.1% of patients who would have been missed by a pH study alone. As indicated in Table 2, belch ($N = 6$, 31.6%) and cough ($N = 6$, 15.7%) were the most prevalent symptoms associated with nonacid reflux.

The results were very similar when symptom-reflux association was considered with the SI, which was positive ($\geq 50\%$) for nonacid reflux only in eight (10.8%) patients who would have been missed by a pH study alone (Fig. 3). As a whole, SI was positive in 42 (56.8%) subjects, 24 (32.4%) for acid reflux only, 8 (10.8%) for nonacid reflux only, and 10 (13.5%) for both. With the SI analysis, 45.9% of the symptomatic subjects had symptoms associated with acid reflux and 24.3% with nonacid reflux.

In this group of subjects, the agreement between SAP and SI was poor ($\kappa = 0.39$).

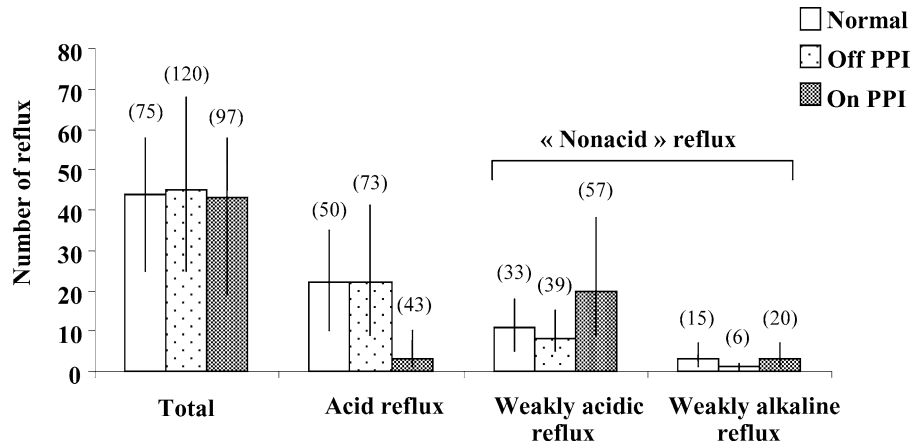


Figure 1. Number and types of gastroesophageal reflux in normal subjects (N = 72) (6) and in patients off PPI (N = 79) and on PPI (N = 71). Bars indicate medians, lines indicate 25th and 75th percentile. Numbers in brackets are 95th percentile values.

RELATIONS BETWEEN NUMBERS OF REFLUX EPISODES AND SYMPTOM ASSOCIATION. Among the three patients with a positive SAP for nonacid reflux only, none had an abnormal total number of reflux or weakly alkaline reflux, and one had a number of weakly acidic reflux above normal values.

Group II: Patients on PPI Therapy

This group consisted of 71 patients, 46 women (64.8%), mean age 51 ± 15, range 16–84 yr. Sixty-eight patients received a double-dose PPI and three received a single dose (esomeprazole 40 mg o.d.). During the monitoring period, 60 patients (84.5%) reported at least one type of symptom, 44 (62.0%) reported two different types of symptoms, and 18 (25.3%) reported three different types of symptoms.

NUMBER AND CHARACTERISTICS OF REFLUX EVENTS. The numbers of different types of gastroesophageal reflux events detected during the pH-impedance studies are indicated in Figure 1. The median number of reflux was very similar to those observed in normals (43 and 44, respectively). However, the median number of acid reflux was very low while the number of weakly acidic reflux was significantly high (3 and 20, respectively). The number of weakly alkaline reflux was similar to normal values

Table 1. Number of Patients with Abnormal Values of Gastroesophageal Reflux and Esophageal Exposure to Volume and Acid as Compared with a Series of Normal Subjects (6)

	Group I (off PPI) N = 79	Group II (on PPI) N = 71
Total number of reflux > 75	16 (20.2%)	6 (8.4%)
Number of acid reflux > 50	15 (18.9%)	1 (1.4%)
Number of weakly acidic reflux > 33	5 (6.3%)	24 (33.8%)
Number of weakly alkaline reflux > 15	5 (6.3%)	6 (8.4%)
Esophageal acid exposure > 5%	17 (21.5%)	5 (7.0%)
Esophageal bolus exposure > 2%	20 (25.3%)	15 (21.1%)

(median 3). The numbers of patients with abnormal values are indicated in Table 1. Twenty-four subjects (33.8%) had an abnormally high number of weakly acidic reflux. Esophageal exposure to volume (bolus exposure) and to acid were above normal values in, respectively, 15 (21.1%) and 5 (7.0%) subjects.

SYMPTOM-REFLUX ASSOCIATION. Sixty subjects reported symptoms during the pH-impedance study. Twenty-two of the symptomatic subjects (36.7%) had positive SAP. The symptom association with acid and nonacid reflux is shown in Figure 4. As shown in Figure 3, pH-impedance monitoring allowed establishing a temporal association between reflux and symptoms in 16.7% of patients who would have been missed by a pH alone study. As indicated in Table 3, regurgitation (N = 13, 35.1%) and cough (N = 5, 20.8%) were the most prevalent symptoms associated with nonacid gastroesophageal reflux.

When symptom-reflux association was considered with the SI, a positive association was found for nonacid reflux only in

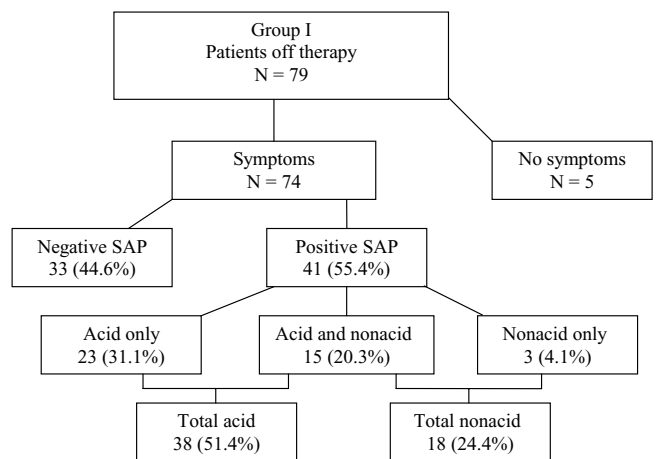


Figure 2. Symptom-reflux association in patients without PPI therapy.

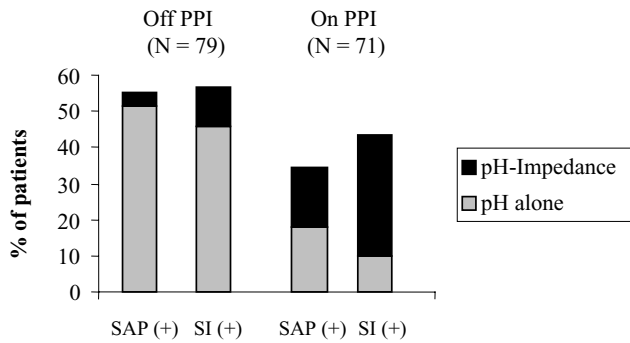


Figure 3. Added value of impedance recording compared with symptom analysis with pH alone. In gray is represented the proportion of patients with symptom associated with acid reflux (detected by a pH fall below 4) and in black additional patients with symptoms associated with nonacid reflux (only detected by pH-impedance) who would have been missed by pH study alone (SAP = symptom association probability, SI = symptom index).

20 (33%) patients who would have been missed by a pH study alone. As a whole, SI was positive in 26 (43.3%) subjects, three for acid reflux (5.0%), 20 for nonacid reflux (33.3%), and 3 (5.0%) for both. With the SI analysis, 8% of the symptomatic subjects had symptoms associated with acid reflux and 38.3% with nonacid reflux.

In this group of subjects, the agreement between SAP and SI was poor ($\kappa = 0.26$).

RELATIONS BETWEEN NUMBERS OF REFLUX EPISODES AND SYMPTOM ASSOCIATION. Among the 10 patients with a positive SAP for nonacid reflux only, one had an abnormal total number of reflux, one an abnormal number of weakly alkaline reflux, and four had a number of weakly acidic reflux above normal values.

DISCUSSION

In this multicenter study performed with a standardized 24-h ambulatory pH-impedance technique, a temporal relationship could be established between symptoms and nonacid reflux alone in 4.1% and 16.7% of the subjects off and on therapy, respectively. These groups of patients represent the

increased diagnostic yield of that technique compared with pH recording alone. Moreover, we have shown that regurgitation and cough were the most prevalent symptoms associated with nonacid reflux in these patients with suspicion of GERD symptoms.

The development of pH-impedance monitoring in routine practice is still at a very early stage; indeed, an analysis of pH-impedance recordings is time consuming and requires experience. Although seven centers were involved, we put efforts to standardize and homogenize the technique as much as possible. For example, all investigators participated in training sessions that aimed at interpretation of recording applying similar definitions and criteria for analysis. Two methods can be used to establish a relationship between reflux and symptoms, *i.e.*, SAP and SI. Because SAP is now considered to be the best method to express the temporal relationship between symptoms and reflux episodes (11), SAP was the main end point for the classification of our patient groups. However, as SI is a simple, easy to determine and understand parameter, we also expressed our results according to this description. A 2-min time window before the onset of symptoms was primarily adopted for symptom analysis as previous works have demonstrated that it was the most appropriate, at least in patients with chest pain (12). Yet we also used a 5-min time window, which may be more appropriate for certain symptoms that lack sudden onset. This large time window also allows comparisons with other impedance-pH studies (9). In this study, as in a previous similar study (9), the agreement between the two methods was poor in patients on and off PPIs (κ values of 0.26 and 0.39, respectively).

The population of patients off PPI that was referred to our centers for diagnostic purposes is very representative of the group of patients with a reasonable suspicion of GERD diagnosis but without typical symptoms. Many of them presented with atypical symptoms and had no evidence of mucosal breaks at endoscopy, although no recent endoscopy was required to be included in the study. The type of patients recruited explains that only 21% of them had an abnormal esophageal acid exposure. This group of patients corresponds largely to the population of subjects frequently submitted to a PPI test and/or treated by PPI empirically. Regarding the group “on PPI,” they had either atypical or typical symptoms

Table 2. Symptom-Reflux Association in 74 Symptomatic Patients off PPI (%)

	Patients (N)	SAP (+) AR (%)	SI (+) AR (%)	SAP (+) NAR (%)	SI (+) NAR (%)
Cough	38	12 (31.6)	10 (26.3)	6 (15.7)	3 (7.9)
Regurgitation	32	13 (40.6)	14 (43.8)	3 (9.4)	7 (21.9)
Heartburn	30	7 (23.3)	13 (43.3)	3 (10.0)	4 (13.3)
Belch	19	10 (52.6)	6 (31.6)	6 (31.6)	1 (5.2)
Chest pain	10	2 (20.0)	2 (20.0)	1 (10.0)	0 (0)
Epigastric pain	9	3 (33.3)	2 (22.2)	0 (0)	0 (0)
Globus, pharyngeal pain	6	2 (33.3)	2 (33.3)	0 (0)	0 (0)
Asthma	6	0 (0)	1 (16.7)	0 (0)	1 (16.7)
Nausea	3	1 (33.3)	0 (0)	0 (0)	0 (0)

SAP = symptom association probability; SI = symptom index; AR = acid reflux; NAR = nonacid reflux.

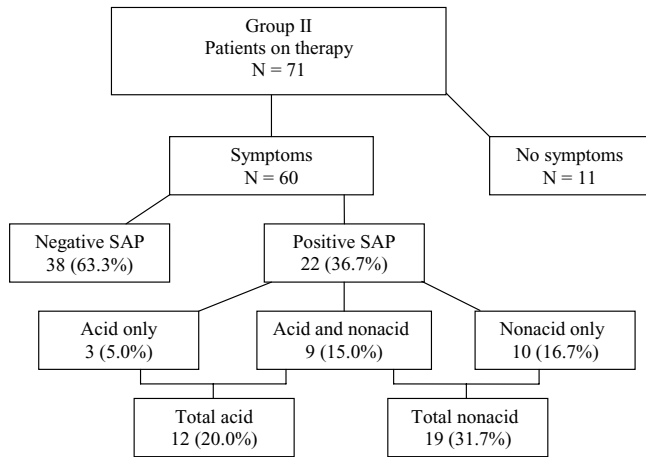


Figure 4. Symptom-reflux association in patients on PPI therapy.

despite adequate acid-suppressive therapy. This refractoriness to PPI may have different causes including poor acid control. Therefore, it has been advocated to perform reflux testing in these patients while on therapy. However, the yield of pH monitoring in these conditions has been reported to be very low by several authors (13, 14).

In patients off therapy, more than 50% of symptomatic patients during the study day had symptoms associated with acid reflux, which is not surprising especially for typical (heartburn and regurgitation) as well as atypical (cough) symptoms. In this group, 24% of symptomatic patients had symptoms associated with nonacid reflux. To our knowledge, this is the first ambulatory 24-h study reporting association of symptoms with nonacid reflux in such a cohort of patients. The most frequently associated symptoms were belch and cough and to a lesser extent heartburn and regurgitation. Bredenoord *et al.* have reported in a series of 32 patients that 15% of symptoms were associated with nonacid reflux (15). Our results are consistent because we observed that approximately 10% of our subjects had a positive SAP for heartburn and regurgitation and nonacid reflux. Recently, Sifrim *et al.* have reported a positive SAP for cough and nonacid reflux in 5 of 22 (23) very selected patients without PPI (7), while we found a positive association in only 15.7% of our subjects. In addition to patient selection, this lower rate may be related to the methods

used to detect cough episodes: manometry was used for precise recognition of cough in Sifrim's study while a classical event marker activated by the patient was used in our study; it has been demonstrated that the event marker is adequately used for only 40% of cough events (7). If symptoms can be associated with nonacid reflux in patients without PPI, it is to note that the majority of the patients in our study had a positive SAP for both acid and nonacid reflux, and that only 4.1% had symptoms exclusively associated with nonacid reflux. The proportion of patients with a positive association using SI is slightly higher (10%). Finally, in clinical practice, combined pH-impedance study in patients off PPI allows establishing a temporal relationship between reflux and symptoms in only 5–10% more than conventional pH recording. Very similar results have been recently reported (16). By contrast, in this group of patients, the analysis of SAP for acid reflux was very effective, showing an association in more than 50% of the subjects while only 20% had an abnormal esophageal acid exposure, and thus demonstrating the high prevalence of the so-called hypersensitive esophagus that belongs in fact to the GERD spectrum (17). These findings underline the importance of symptom analysis when interpreting pH data. If done appropriately, impedance monitoring adds little value to the diagnostic yield.

The results obtained in patients on PPI are quite different. First, the majority of patients (two-thirds) experienced symptoms during the study day that could not be associated with any type of gastroesophageal reflux by the means of ambulatory pH-impedance monitoring. Therefore, in these patients, the hypothesis of GERD as a cause of their symptoms should reasonably be abandoned. Second, 16.7% (SAP positive) to 33.3% (SI positive) of the patients had a significant temporal correlation between symptoms and nonacid reflux only. These results are consistent with those recently reported by Mainie *et al.* who observed 37% of patients with a positive SI for nonacid reflux (9).

Regurgitation (35%) and cough (21%) were the most prevalent symptoms associated with nonacid reflux while a relatively low proportion of patients (8%) had heartburn associated with nonacid reflux. In a stationary study, Vela *et al.* also reported that heartburn was associated with only 10% of nonacid reflux events in patients treated with omeprazole (8). Only a minority of patients in our study reported ENT

Table 3. Symptom-Reflux Association in 60 Symptomatic Patients on PPI (%)

	Patients (N)	SAP (+) AR	SI (+) AR	SAP (+) NAR	SI (+) NAR
Heartburn	41	2 (4.9)	2 (4.9)	3 (7.3)	4 (9.8)
Regurgitation	37	7 (18.9)	4 (10.8)	13 (35.1)	13 (35.1)
Cough	24	1 (4.2)	0 (0)	5 (20.8)	0 (0)
Chest pain	13	0 (0)	0 (0)	1 (7.7)	1 (7.7)
Globus, pharyngeal pain	7	0 (0)	1 (14.2)	0 (0)	0 (0)
Epigastric pain	6	0 (0)	1 (16.7)	0 (0)	0 (0)
Belch	2	1 (50.0)	0 (0)	1 (50.0)	1 (50.0)
Asthma	2	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)
Nausea	1	0 (0)	0 (0)	0 (0)	1 (100.0)

SAP = symptom association probability; SI = symptom index; AR = acid reflux; NAR = non-acid reflux.

symptoms (e.g., globus, pharyngeal pain, and hoarseness), which were virtually never associated with reflux. A large prospective randomized study recently showed that ENT symptoms were not significantly improved by a double-dose PPI therapy, suggesting that the relationship between these symptoms and acid reflux is unlikely (18). The hypothesis that ENT symptoms could be related to a persistent nonacid gastroesophageal reflux has been proposed but is not supported by our data. In fact, the link between reflux and ENT symptoms can hardly rely on symptom-reflux association analysis because these symptoms are usually long lasting (or permanent) and do not have a sudden onset that could be easily perceived by the patient. Studies with antireflux therapies able to reduce nonacid reflux such as surgery or baclofen (19, 20) are mandatory to further elucidate this issue.

Considering the diagnostic yield of pH-impedance monitoring in patients on PPI, a positive association with nonacid reflux only was observed in 16.7% of patients who would have been misdiagnosed by a pH alone study. This proportion is substantially higher (33%) when the symptom-reflux association is analyzed with the SI. We believe that SAP explores more adequately than SI the relationships between reflux and symptoms, but a statistically significant relationship between two parameters does not necessarily imply causality. A recent study in a small cohort has shown that a positive association between nonacid reflux and symptoms could predict a favorable outcome after fundoplication (21).

In conclusion, this study demonstrates that symptoms suggestive of GER can be associated with nonacid reflux detected with combined pH-impedance monitoring in patients with and without any acid suppressive therapy, mainly regurgitation and cough. Adding impedance to pH monitoring improves the diagnostic yield and allows better symptom analysis than pHmetry alone, mainly in patients on PPI therapy. The actual impact of pH-impedance monitoring on GERD management remains to be investigated by prospective outcome studies based on symptom-reflux association analysis.

ACKNOWLEDGMENT

This study was supported by CRITERE (Consortium de Recherche Indépendant sur le Traitement et l'Exploration du Reflux Gastro-œsophagien et de l'Endobranchyœsophage). All the authors are members of CRITERE. We are indebted to Ms. Maylis Capdepon for her help in statistical analysis.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Acid gastroesophageal reflux plays a major role in eliciting gastroesophageal reflux symptoms.
- Esophageal pH monitoring is the gold standard for the diagnosis of gastroesophageal reflux.

- Combined esophageal pH-impedance monitoring allows detection of acid as well as non-acid reflux.
- The role of non-acid reflux in the pathogenesis of symptoms is poorly known.

What Is New Here

- In patients off proton pump inhibitors, pH-impedance monitoring adds little value to the diagnostic yield as compared with pH recording alone (5-10%).
- In patients on proton pump inhibitor therapy, adding impedance to pH monitoring improves the diagnostic yield and allows better symptom analysis than pHmetry alone.
- The symptoms most frequently associated with non acid reflux are cough and regurgitation.

Reprint requests and correspondence: Frank Zerbib, M.D., Ph.D., Gastroenterology Department, Saint Andre Hospital, 1, rue Jean Burguet, 33075 Bordeaux, France.

Received February 11, 2006; accepted April 4, 2006.

REFERENCES

1. Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastric reflux in esophageal mucosal injury: A review of animal and human studies. *Gastroenterology* 1995;108:1897-907.
2. Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis. *Gastroenterology* 1997;112:1798-810.
3. Castell DO, Kahrilas PJ, Richter JE, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. *Am J Gastroenterol* 2002;97:575-83.
4. 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.
5. Shay S, Tutuian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: A multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol* 2004;99:1037-43.
6. Zerbib F, Bruley des Varannes S, Roman S, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. *Aliment Pharmacol Therap* 2005;22:1011-21.
7. Sifrim D, Dupont L, Blondeau K, et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut* 2005;54:449-54.
8. 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.
9. Mainie I, Tutuian R, Shay S, et al. Acid and nonacid reflux in patients with persistent symptoms despite acid suppressive therapy. A multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 2006. Published Online First: 23 March 2006. doi:10.1136/gut.2005.087668.

10. 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.
11. Bredenoord AJ, Weusten BL, Smout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. *Gut* 2005;54:1810–7.
12. Lam HG, Breumelhof R, van Berge Henegouwen GP, et al. Temporal relationships between episodes of non-cardiac chest pain and abnormal oesophageal function. *Gut* 1994;35:733–6.
13. Tack J, Koek G, Demedts I, et al. Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: Acid reflux, bile reflux, or both? *Am J Gastroenterol* 2004;99:981–8.
14. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol* 2005;100:283–9.
15. Bredenoord AJ, Weusten BL, Curvers WL, et al. Determinants of perception of heartburn and regurgitation. *Gut* 2006;55:313–8.
16. 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.
17. Shi G, Bruley des Varannes S, Scarpignato C, et al. Reflux related symptoms in patients with normal oesophageal exposure to acid. *Gut* 1995;37:457–64.
18. Vaezi MF, Richter J, Stasney R, et al. A randomized, double-blind, placebo-controlled study of acid suppression for the treatment of suspected laryngo-pharyngeal reflux. *Gastroenterology* 2004;126(suppl 2):A22.
19. Vela MF, Tutuian R, Katz PO, et al. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Therap* 2003;17:243–51.
20. Sifrim D, Zhang X, Rydholm H, et al. Baclofen reduces weakly acidic reflux in ambulant patients with GERD. *Gastroenterology* 2005;128:A531.
21. Mainie I, Tutuian R, Agrawal A, et al. Persistent typical and atypical GERD symptoms on PPI therapy are produced by different mechanisms. *Gastroenterology* 2005;128:A386.

The authors declared no conflicts of interest.
