Dig Dis Sci (2013) 58:2556–2563
DOI 10.1007/s10620-013-2672-3

ORIGINAL ARTICLE

Prolonged 2-Day Esophageal pH-Metry with Impedance Monitoring Improves Symptom-Reflux Association Analysis

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Received: 15 January 2013 / Accepted: 27 March 2013 / Published online: 16 April 2013

Abstract
Background The day-to-day variability in the number of reflux episodes and symptoms of gastro-esophageal reflux disease is high; therefore, the assessment of reflux disease based on 24-h monitoring may be inaccurate.
Aims The aim of the study was to compare prolonged (48 h) and standard (24 h) pH-impedance monitoring (pH-MII).
Methods Fifty-four consecutive patients with typical and atypical reflux symptoms underwent 48-h pH-MII. Acid exposure time (AET), total number of reflux episodes (TR), number of symptoms, and symptom association probability (SAP) were analyzed after the first 24 h and compared with the results obtained during 48 h of monitoring.
Results The differences between the fractions of patients with normal and abnormal total AET and TR on both days were not significant. The percentage of patients with positive SAP was 57.9 % at 24 h and 71.9 % at 48 h (difference: 14.81 %, 95 % CI 0.7–21.29, $P < 0.05$). There were ten patients (10/54, 18.5 %) with positive SAP after 48 h that had been negative in the first 24 h. In comparison to 24 h monitoring, patients reported a significantly increased number of various symptoms correlated with reflux after 48 h.
Conclusions Extending pH-MII monitoring to 48 h does not improve the detection of abnormal acid exposure. However, it does increase the fraction of patients with positive symptom-reflux association by as much as 18.5 %.

Keywords Esophageal pH monitoring · Gastro-esophageal reflux · Impedance · Symptom assessment

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Introduction

Reflux monitoring with esophageal 24-h pH-metry has traditionally been based on measuring the abnormal esophageal acid exposure time (AET) and the number of acid reflux episodes [1]. However, the sensitivity of the pH test is limited by the day-to-day variability in AET. Up to 16 % of patients with a positive 24-h pH monitoring had negative results on the follow-up 24-h pH-metry [2]. Moreover, up to 25 % of subjects with erosive esophagitis have a false negative pH-metry result, and the number of negative pH tests may be even higher in patients with non-erosive reflux disease (NERD) [3]. The false negative 24-h pH-metry may be a consequence of changes in daily activities and food consumption during a pH test, resulting in detecting a lower number of acid reflux episodes and symptoms. In some patients, these changes may be due to a poor tolerance to the trans-nasal placement of the pH catheter [4, 5]. These limitations have been overcome by the development of a wireless esophageal pH test that also allows for prolonged pH recording. Extending the monitoring period from 24 to 48 h increases the sensitivity of the pH test by 10–26 %, thereby improving symptom analysis as an increased number of symptoms is reported by patients with a longer duration of recording. Although the wireless system is generally well tolerated, the disadvantages include: chest discomfort, premature detachment, necessity of using endoscopy, and poor availability [6–9].

Additionally, the potential limitations of pH-tests are: (1) low sensitivity in detecting reflux with pH above 4.0 and (2) lack of the assessment of correlation of symptoms with non-acid reflux episodes.

Combined pH with impedance monitoring is the only available method with the ability to quantify acid and non-acid reflux, which increases the diagnostic yield of gastro-esophageal reflux disease (GERD) by 15–20 % [10–13]. Compared to pH-metry-only evaluation, the greatest asset of pH-impedance monitoring is the possibility to assess those patients with persistent symptoms despite proton pump inhibitor (PPI) therapy [12–17]. pH-impedance is also helpful in evaluating patients with NERD and extra-esophageal reflux symptoms [13, 16, 18–21]. Both groups represent the most problematic patients in clinical practice.

Taking into consideration the day-to-day variability in reflux and symptoms, and the occurrence of non-acid reflux, the 24- or 48-h pH-only monitoring can be inaccurate in assessing some patients with refractory symptoms despite PPI therapy or NERD patients with extraesophageal reflux symptoms. Therefore, the aim of our study was to compare the prolonged (48 h) pH and impedance monitoring (pH-MII) with a standard 24-h test.

Methods

Patients

We performed a retrospective analysis of prolonged pH and impedance tests that were conducted in 57 consecutive patients. The patients were referred to the Department of Gastroenterology and Internal Medicine at the Medical University of Bialystok for pH-impedance monitoring due to persistent GERD symptoms despite PPI therapy, and for the evaluation of extraesophageal GERD symptoms. The patients reported typical (heartburn, regurgitation) and atypical (chest pain, abdominal pain, belching, cough) reflux symptoms. In patients exhibiting persistent symptoms despite PPI treatment for a period of at least 2 months (with previously documented GERD: typical reflux syndrome, and/or esophagitis, and/or abnormal acid exposure off PPI therapy), pH-MII monitoring was performed on the continued twice daily standard dose of PPI therapy. In patients who were referred for the evaluation of potential association of extraesophageal reflux symptoms with GERD, to exclude or to confirm GERD as a cause of symptoms, pH-MII monitoring was performed off PPI therapy. Other causes of extraesophageal symptoms were excluded by cardiologists, allergologists, and laryngologists before referral. Exclusion criteria included a history of previous gastric or esophageal surgery, and esophageal motility disorders. Upper gastrointestinal endoscopy was performed in all patients within the last 12 months or before pH-MII monitoring. Both the study protocol and all the procedures were approved by the Local Ethics Committee of the Medical University in Bialystok, and all the subjects gave their informed written consent before the start of any procedure.

pH-Impedance Monitoring

pH-MII monitoring was performed after an overnight fast using a Sleuth multi-channel intraluminal impedance system (Sandhill Scientific Inc., Highland Ranch, CO), consisting of a portable data logger and a catheter with one pH electrode and eight impedance electrodes at 3, 5, 7, 9, 15, and 17 cm from the tip, positioned 5 cm above the upper border of the lower esophageal sphincter (LES) as determined by manometry. The patients were instructed to press the event marker button on the data logger whenever they experienced a symptom and to fill out a diary indicating the time of the symptom, the start and end times of their meals, changes in body position (recumbent, upright), and time of PPI intake. The patients were asked to consume at least three meals during the day and encouraged to try to maintain their normal daily routine. Meal periods were excluded from analysis. All data was collected on 256 MB compact flash cards. After 48 h of monitoring (the time of monitoring included two nights), the data was downloaded onto a computer and analyzed using a semi-automated software system (BioView, Sandhill Scientific) and verified manually.

Data Analysis

The following data was analyzed: acid exposure time (AET), acid clearance time (ACT), bolus clearance time (BCT), number of reflux episodes (TR), number of reflux episodes reaching 15 cm above LES (proximal reflux), and the number of symptoms. Total acid exposure time (% total time at pH below 4.0) of less than 4.2 % over 24 h was considered normal for patients off PPI therapy, while less than 1.3 % was considered a norm for patients on PPI therapy, in accordance with previously published criteria [22, 23]. Reflux episodes were classified as acid, weakly acidic, or weakly alkaline in accordance with previously reported criteria: (1) acid reflux: impedance-detected reflux with nadir pH below 4; (2) weakly acidic reflux: reflux with nadir pH between 4 and 7; (3) weakly alkaline reflux: reflux with nadir pH above 7.

The number of symptoms related to acid reflux and weakly acidic reflux, as well as weakly alkaline reflux was calculated. Symptom-reflux association was performed using SI (symptom index) and SAP (symptom association probability) indexes for each patient. Separate analysis was performed for each individual symptom if the patient

recorded symptoms of different types. The patient was considered as a patient with positive symptom-reflux association if he/she had at least one type of symptom correlated with reflux. For each patient, the number of different types of symptoms with positive reflux association was calculated. The SI and SAP were calculated according to the formula described by other authors [24, 25]. The SI was defined as the percentage of reflux-related symptoms preceded by reflux (with 2-min time window). The SAP was calculated by dividing the data set into consecutive 2-min periods. We investigated whether reflux episodes occurred in each 2-min segment and in the 2-min period before each symptom. SAP indicates the statistical probability that the observed symptom-reflux association could have occurred by chance. The cutoff value for a positive SAP test was SAP $\geq$95 % and for the SI test $\geq$50 %.

All parameters were analyzed separately for the first and second 24 h of monitoring (day 1 and day 2). Data measured during the first 24 h were compared to the final outcome after 48 h of monitoring (day 1 + 2). All analyses were performed on all the patients participating in the study and, additionally, on two subgroups of patients: off PPI therapy and on PPI therapy.

At the end of the pH-impedance test, all patients were asked to answer the following three questions: "Did you tolerate the study well?", "Did you experience any side effects associated with the probe?", and "Would you do the test again?".

Statistical Analysis

Not-normally distributed data obtained from the subjects were summarized by median values and interquartile ranges (IQRs) and comparisons between them on day 1 and day 2 were performed using the Wilcoxon matched-pairs signed-rank test. The differences between the fractions of patients (expressed as a percentage with a 95 % confidence interval [CI]) with positive and negative SI and SAP, normal and abnormal AET, and normal and abnormal total number of reflux episodes in each period of the study time were performed using the McNemar exact testing. Differences were considered statistically significant when $P < 0.05$. All statistical analyses were performed using STATA statistical software.

Results

Patients and Technical Success of 48-h pH-MII Monitoring

Fifty-seven patients (median age 49, 20–72 years, 32 females) agreed to undergo pH and impedance monitoring for 48 h. One patient did not complete the two-day-long study due to the failure of the monitoring device battery. One patient was excluded from analysis due to a technical problem with the pH electrode. In one patient, the probe was disconnected from the Sleuth device at night. Therefore, complete two-day-long recordings were available for 54 patients (94.7 %).

In 33 patients, pH-MII monitoring was performed off PPI therapy. Endoscopy showed erosive esophagitis in eight of those patients (8/33; 24.2 %; grade A in six patients and grade B in two patients according to Los Angeles classification), ESEM (endoscopically suspected esophageal metaplasia) in one patient (1/33; 3 %), and hiatal hernia in five patients (5/33; 15.2 %).

In 21 patients with previously diagnosed GERD and refractory reflux symptoms, pH and impedance monitoring were performed on PPI therapy. Among those 21 patients without erosive esophagitis, four patients (4/21; 19 %) had hiatal hernia.

pH-MII monitoring was well tolerated by all subjects with the exception of eight patients (8/54; 14.8 %): three patients had throat pain (two on day 1 and one on day 2) and five experienced nasal discomfort during monitoring (two on day 1 and three on day 2). Importantly, 76 % of the patients would do the test again. The median duration of recording was 45.82 h (IQR 45.13–47.09).

Reflux Episodes

The characteristics of reflux episodes are presented in Table 1. Compared with reflux episodes on day 1, reflux episodes on day 2 had similar characteristics except for the median number of acidic reflux episodes, which occurred more frequently on day 1. This difference was detectable in patients on PPI therapy, but not in patients who were off-therapy (data not shown). The abnormal total number of reflux episodes on both day 1 and day 2 was reported by 29.6 % (16/54) of patients. Furthermore, 64.8 % (35/54) had normal total number of reflux episodes on both days of monitoring. There were no significant differences between the fractions of patients with abnormal and normal number of reflux episodes documented on day 1 and day 2 (1.85 %; 95 % CI −4.51 to 5.46; $P = 1.000$; Fig. 1).

Esophageal Acid Exposure Time, Acid Clearance Time, and Bolus Clearance Time

The median total AET, ACT, and BCT on day 1 were similar to day 2 in all patients (Table 2). Overall, 81.5 % (44/54) of patients had similar AET on both days 1 and 2. There was no concordance of AET measurement between both days in 18.5 % (10/54) of patients (Fig. 1). There were no significant differences between the fractions of

Table 1 Characteristics of reflux episodes

The study group ($n = 54$)	Day 1, median (25–75 %)	Day 2, median (25–75 %)	P	Day 1 and day 2, median (25–75 %)
Total reflux episodes	48 (36–73)	48 (34–67)	0.1231	97 (73–138)
Acidic reflux	24 (14–42)	21.5 (11–39)	0.0280	44.5 (27–79)
Weakly acidic reflux	17.5 (12–31)	17 (12–37)	0.2244	33 (25–53)
Weakly alkaline reflux	0 (0–1)	0 (0–2)	0.4799	1 (0–3)
Proximal reflux	22 (14–41)	23.5 (16–36)	0.8767	42 (27–75)

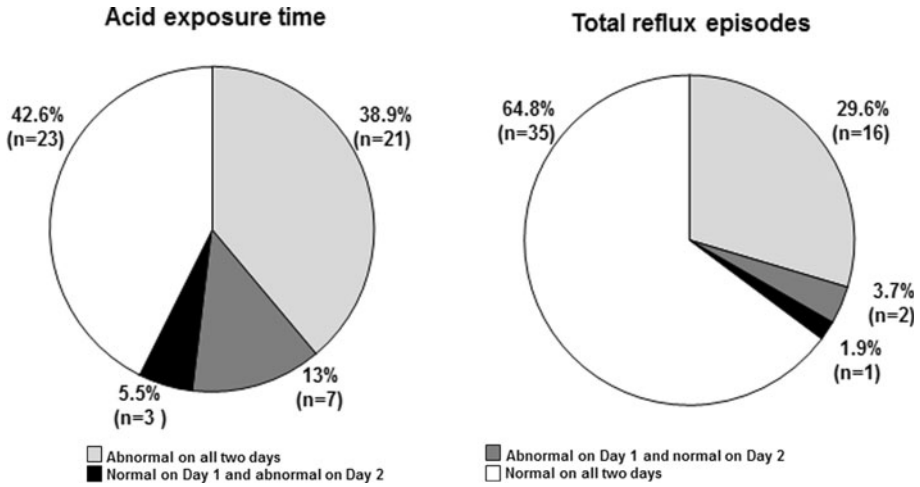

Fig. 1 Day-to-day distribution of abnormal and normal total acid exposure time and total reflux episodes. *n* number of patients

patients with normal and abnormal total AET documented on day 1 and day 2 (7.41 %; 95 % CI −5.65 to 16.05 %; $P = 0.3438$).

Symptoms Reported by Patients

There were only two patients who did not report symptoms during the first day, but had symptoms during the second day of monitoring. One patient with symptoms on day 1 did not report symptoms on day 2. Overall, a median number of 11 (IQR 6–26), 9.5 (IQR 5–32), and 21 (IQR 10–58) symptoms per patient was reported during day 1, day 2, and after 2 days of monitoring, respectively. The following symptoms were reported by the patients: heartburn (37 %; 20/54), regurgitation (48 %; 26/54), abdominal pain (46.3 %, 25/54), chest pain (42.6 %, 23/54), and belching (59 %; 32/54).

Symptom-Reflux Association in All Patients

When symptom-reflux association was analyzed separately for the first and second 24-h period of monitoring, a significant difference was found in the number of patients with positive SI [day 1: 68.5 %, (37/54) vs. day 2: 81.5 % (44/54), difference: 12.96; 95 % CI 0.58–16.57; $P = 0.0391$]. There was no difference between day 1 and day 2 in the percentage of patients with positive SAP [day 1: 59.2 %, (32/54) vs. day 2: 63 %, (34/54), difference: 3.7 %; 95 % CI −12.83 to 18.98; $P = 0.8145$] (Fig. 2).

However, we found significant differences in the number of patients with positive SI or SAP on the first day and after 2 days of monitoring. The percentage of patients with positive SI was 68.5 % (37/54) on day 1 and 87.0 % (47/54) on days 1 + 2 (difference: 18.52 %; 95 % CI 2.58–27.23; $P = 0.0213$). The percentage of patients with positive SAP was 59.2 % (32/54) on day 1 and 74.1 % (40/54) on days 1 + 2 (difference: 14.81 %, 95 % CI 0.7–21.29; $P = 0.0386$; Fig. 3).

Symptom-Reflux Association in Subgroups of Patients Off and On PPI Therapy

No significant differences in the number of patients with positive SI or SAP during the first 24 h and following 2 days of recording were found in patients on PPI therapy upon analyzing the symptom-reflux association separately in both the off- and on-PPI therapy subgroups of patients. The percentage of patients tested on PPI therapy with positive SI was 71.4 % (15/21) on day 1 and 81.0 % (17/21) on days 1 + 2 (difference: 9.52 %, 95 % CI −11.65 to 18.81, $P = 0.6250$). The percentage of patients tested on PPI therapy with positive SAP was 66.7 % (14/21) on day 1 and 72.6 % (16/21) on days 1 + 2 (difference: 9.52 %, 95 % CI −11.65 to 18.81, $P = 0.6250$). However, the

Table 2 pH-MII parameters in relation to the duration of analysis and treatment with proton pump inhibitor

The study group ($n = 54$)	Day 1, median (25–75 %)	Day 2, median (25–75 %)	*P*
Duration of analysis (s)			
Total	22 (21.2–22.52)	22.03 (21.02–22.36)	0.6620
Upright	12.04 (10.28–13.24)	12.17 (10.51–13.11)	0.8341
Recumbent	9.39 (8.53–10.81)	9.52 (8.46–11.29)	0.9709
AET total (%)	2.45 (0.7–5.3)	1.9 (0.6–4.4)	0.0974
ACT total (sec)	89.5 (38.0–161.0)	88.0 (46.0–130.0)	0.1201
BCT total (sec)	11.05(9.0–15.0)	11.0 (8.0–13.0)	0.7505
On PPI ($n = 21$)			
AET total (%)	0.6 (0.0–2.1)	0.4 (0.1–0.8)	0.0677
ACT total (sec)	68.0 (24.0–92.0)	50.0 (37.0–93.0)	0.8077
BCT total (sec)	10.0 (7.0–15.0)	11.0 (8.0–13.0)	0.3103
Off PPI ($n = 33$)			
AET total (%)	4.5 (1.4–7.6)	3.7 (2.0–6.0)	0.3301
ACT total (%)	132.0 (52.0–204.0)	95.0 (68.0–173.0)	0.2640
BCT total (%)	12.0 (10.0–15.0)	12.0 (9.0–13.0)	0.3895

AET acid exposure time, *ACT* acid clearance time, *BCT* bolus clearance time, *PPI* proton pump inhibitor

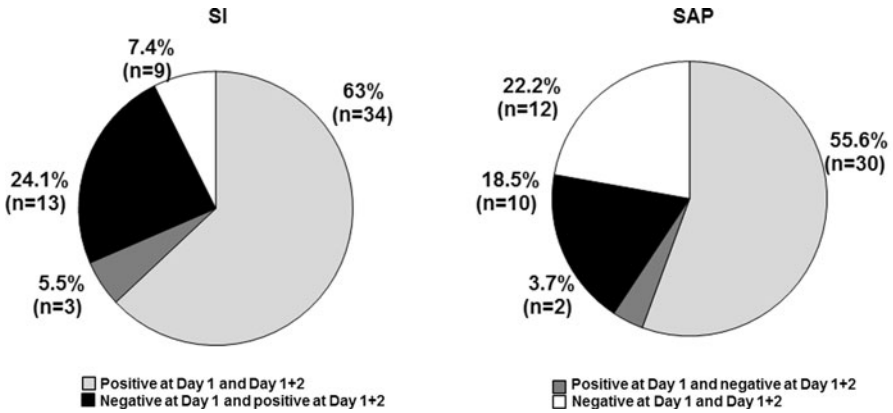

Fig. 2 Symptom-reflux association in relation to the duration of pH-MII monitoring. *SI* symptom index, SI positive ≥50 %, SI negative <50 %. *SAP* symptom association probability, SAP positive ≥95 %, SAP negative <95 %

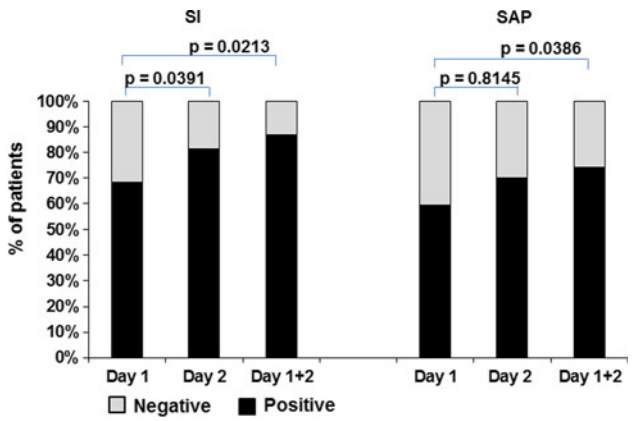

Fig. 3 Day-to-day distribution of positive and negative symptom-reflux association: symptom index and symptom association probability. *n* number of patients, *SI* symptom index, SI positive ≥50 %. *SAP* symptom association probability, SAP positive ≥95 %

difference in the percentage of patients with positive SI on day 1 and days 1 + 2 was significant in patients off PPI therapy [24.4 %, day 1: 66.7 % (22/33) vs. days 1 + 2: 90.9 % (30/33), 95 % CI 1.15–34.85, $P = 0.0386$]. The difference in the percentage of patients tested off PPI therapy with positive SAP on day 1 and days 1 + 2 was not significant [18.18 %, day 1: 54.5 % (18/33) vs. days 1 + 2: 72.7 % (24/33), 95 % CI −1.29 to 24.09, $P = 0.0703$].

Characteristics of Patients with Negative SI or SAP on Day 1 and Positive SI or SAP on Days 1 + 2

Out of the total number of patients, 13 (24.1 %) subjects were found to have a negative SI on the first day of assessment followed by a positive SI after 2 days of monitoring. Only three of those 13 subjects were patients

with refractory GERD symptoms tested on PPI therapy. Among all the patients, ten individuals (18.5 %) had a negative SAP on day 1 and a positive SAP after 2 days of monitoring (Fig. 3). All patients with positive SAP also had positive SI. Seven of those 10 (70 %) subjects were patients off-PPI therapy and all had normal endoscopy findings. Five of the above-mentioned seven patients had abnormal acid exposure time and positive SAP for typical symptoms in only one case, for both typical and atypical symptoms (chest pain, cough, belching) in two cases, and for atypical symptoms (cough, chest pain) in only two patients. These patients were diagnosed as having NERD.

Two of the ten patients with positive SAP had symptoms correlated with acidic reflux alone, three patients had symptoms correlated with acidic and weakly acidic reflux, and five patients with weakly acidic reflux alone.

Association of Symptoms of Different Types with Reflux

In comparison to the one-day assessment, patients reported a significantly increased number of various symptoms correlated with reflux episodes (positive SAP) following 2 days of monitoring (Fig. 4).

Discussion

To the best of our knowledge, our study was the first to demonstrate the potential of esophageal pH with impedance monitoring recorded over a period of 48 h.

The sensitivity of catheter-based 24-h pH-metry is limited by the day-to-day variability in AET, number of reflux episodes, and the number of symptoms reported by the patients [26]. It has been suggested that pH monitoring using a wireless capsule generates less adverse symptoms than the traditional catheter-based system [7–9, 27].

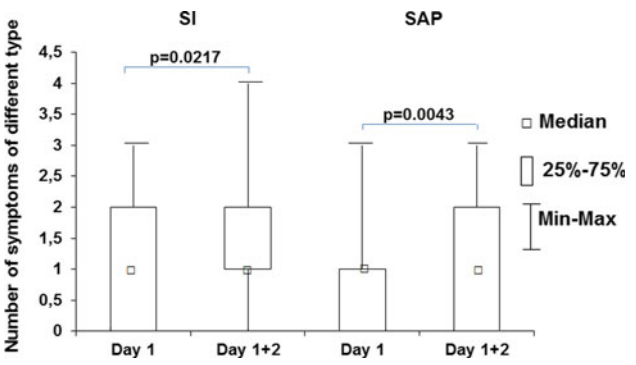

Fig. 4 The number of symptoms of different type with positive symptom-reflux association in subgroups of patients off proton pump inhibitor therapy. *SI* symptom index, *SAP* symptom association probability

However, 10–40 % of patients investigated with a capsule-based protocol experienced symptoms including chest discomfort or foreign body sensation and up to 4 % of them may require endoscopic removal of the capsule due to severe chest pain. Additionally, endoscopy needs to be performed to ensure the proper placement in the esophagus and to assess the gastro-esophageal junction [7, 28–31]. Although a catheter-based study is not well tolerated in up to 10 % of the patients and may affect activity, endoscopy is not necessary. Furthermore, compared to the catheter-based system, the wireless capsule is less available. Our study showed that prolonging monitoring using pH-MII is generally well tolerated. Minor adverse symptoms such as throat pain and nasal discomfort were reported by 14.8 % of the patients. However, 76 % of all patients stated that they would undergo the test again.

Extending pH monitoring to 48 h by using a wireless system improves the detection of abnormal AET by 22 % and increases the sensitivity of the pH test [7, 8, 31, 32]. In comparison, pH-MII monitoring allows for the identification of all acidic, weakly acidic, and weakly alkaline reflux, thereby increasing the diagnostic yield by 15–20 % [10–13]. In our study, we did not demonstrate any significant differences between the 2 days of pH-MII monitoring in the percentage of patients with normal and abnormal results of AET and reflux episode numbers.

An abnormal number of reflux episodes or increased AET do not automatically imply that reflux is the cause of the symptoms, and normal study does not exclude reflux as a cause of the symptoms. In clinical practice, the assessment of the association between reflux and symptoms is more important. There are limitations to the most common indices used for assessing the correlation [33]. SI is defined as the percentage of symptoms that are reflux related, regardless of the total number of reflux episodes. Therefore, patients with a lower number of symptoms have a higher probability of having positive SI. SAP was developed to overcome the limitations of SI [24, 25]. When a patient reports single, rare symptoms, it is difficult or even impossible to assess their correlation with reflux; even 24-h monitoring may not be sufficient. A prolonged wireless pH test improves the symptom-acid reflux correlation [8, 26, 31]. Our study demonstrated that the number of various symptoms increased over time; therefore, indicating that the 2-day test makes the symptom-reflux association more useful. There were ten patients (18.5 %) with positive SAP and 13 patients (24.1 %) with positive SI after 48 h that had been negative in the first 24 h. Such results were particularly evident in patients with atypical symptoms, in whom a pH-MII test was performed to confirm or exclude GERD as a cause of symptoms. We recognized NERD in five of seven patients tested off PPI therapy and with positive SAP only after 2 days of monitoring. In addition,

four out of five of those patients had positive SAP for atypical symptoms. Additionally, two patients met the criteria for functional heartburn. Five out of ten patients with positive SAP after 2 days of monitoring had symptoms correlated with weakly acidic reflux alone, which would not be detected by 24- or 48-h pH study.

Taking into consideration potentially decreased oral intake and physical activity during the catheter-based test, as well as day-to-day variations in reflux episodes and symptom numbers, prolonged monitoring may facilitate diagnosis in patients with a negative 24-h pH study. Sweis et al. [34] demonstrated that prolonged, wireless pH-monitoring increases test sensitivity and diagnostic yield in patients with continuing esophageal symptoms despite negative 24-h catheter pH-studies and concluded that without a definitive diagnosis many would not have received effective treatment. In this study, a good outcome was reported by ten out of 12 patients who underwent anti-reflux surgery. Additionally, there is data demonstrating the clinical usefulness of prolonged wireless pH monitoring in off-PPI treatment evaluation [31, 35] and the pH-MII test for better characterization of patients with persistent symptoms despite PPI therapy [12–21, 36–38]. The utility of prolonged pH-MII monitoring, including the period off and on PPI therapy, might be an issue worthy of future study.

Our study had a number of limitations. The time of monitoring among the individual patients differed slightly, although not significantly. All the patients that completed 2 days (2 nights) were included in the study; also, the minimum time of recording (21 h for each scheduled 24 h period) was achieved. However, there are no standard values for the 48-h pH-impedance monitoring, and the results of this study should be interpreted with caution. Moreover, clinical significance of weakly acidic reflux detected by pH-impedance test remains an area of controversy. Most importantly, we should also take into consideration that increasing the diagnostic yield of the study may also increase false positives. Positive predictive values may likely decrease with additional testing and may best serve to exclude GERD [33]. Future studies should also evaluate whether making symptom-reflux correlation analysis more efficient can influence the effects of therapy.

In summary, our study demonstrated that prolonged 48-h pH-MII monitoring is possible and generally well tolerated. Extending pH-MII monitoring to 2 days does not improve the detection of abnormal acid exposure. However, it does increase the reported number of various symptoms with positive reflux association and the fraction of patients with positive SAP by as much as 18.5 %. It may be considered in patients with normal endoscopy who report rare or atypical symptoms in order to exclude or confirm GERD as a causative factor. A direct comparison of prolonged 48-h pH-impedance with wireless 48-h pH-monitoring, that takes into account all their advantages and disadvantages, should constitute the subject of future studies.

Conflict of interest None.

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