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Addition of Esophageal Impedance Monitoring to pH Monitoring Increases the Yield of Symptom Association Analysis in Patients off PPI Therapy

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BACKGROUND: The additional yield of esophageal impedance monitoring in identification of reflux as the cause of reflux symptoms is unknown.

OBJECTIVES: To compare the yield of symptom–reflux association analysis of combined esophageal pH-impedance data with the yield of analysis of pH data alone.

METHODS: In 60 patients with symptoms of heartburn and regurgitation combined, 24-h pH-impedance monitoring was performed. Acid-suppressive medication was stopped 1 wk in advance. Patients (48) with at least one symptom during the measurement period were selected for further analysis. Patients were instructed to note the time and nature of their symptoms. Eleven types of reflux episodes were defined, based on combinations of magnitude of the pH drop, nadir pH, and nature of the refluxate (gas and liquid) on impedance tracings. Symptom association analysis—symptom index, the symptom sensitivity index, and the symptom association probability (SAP)—was performed for each definition of reflux.

RESULTS: The proportion of patients with a positive SAP ($\geq$95.0%) varied between 62.5% and 77.1%, depending on the definition of reflux episodes. When both pH and impedance parameters were used to identify reflux, a higher proportion of patients had a positive SAP than with pH alone (77.1% *vs* 66.7%, $p < 0.05$). Symptom association analysis for acidic and weakly acidic reflux separately did not result in a higher yield than analysis with all reflux episodes pooled, regardless of pH.

CONCLUSION: In patients off proton pump inhibitor, the addition of impedance monitoring to esophageal pH monitoring leads to an increase in the proportion of patients in whom an association between reflux episodes and symptoms can be identified.

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INTRODUCTION

The gold standard for assessment of the relationship between symptoms of gastroesophageal reflux such as heartburn and regurgitation and reflux episodes is 24-h pH-metry with symptom association analysis (1–3). In a subset of patients no clear relationship is found between the onset of symptoms and the occurrence of gastroesophageal reflux, defined as pH drops below 4. It has been suggested that in some of these patients symptoms are induced by reflux episodes associated with only small changes in pH and a nadir pH above 4 (4). However, until recently, this hypothesis could not be tested since these reflux episodes could not be detected by means of pH-metry.

Some years ago, multiple intraluminal impedance monitoring was introduced as a new and reproducible technique to detect gastroesophageal reflux (5, 6). Detection of gastroesophageal reflux with this technique is irrespective of its acidity, which makes that also reflux with a nadir pH above 4 can be detected (7). Studies using intraluminal impedance monitoring have shown that approximately one third of all reflux episodes are weakly acidic in patients off therapy (8). In a 2-h study of five patients with gastroesophageal reflux disease (GERD), Vela *et al*. showed that weakly acidic reflux episodes could also induce symptoms of heartburn and regurgitation (9). However, in patients who do not use acid secretion inhibitors, only a minority of symptoms seems to be induced by weakly acidic reflux (10). It is thus uncertain whether detection of these episodes with impedance monitoring will increase the yield of symptom association analysis. Therefore, the aim of this study was to investigate the yield of addition of impedance monitoring to pH monitoring in patients with symptoms suspected for GERD.

METHODS

Subjects

In 60 patients with typical reflux symptoms (32 males; aged 28–73 yr, median 49 yr) ambulatory combined impedance and pH monitoring was performed. Those with at least one symptom of heartburn, regurgitation, or chest pain during the measurement period were selected for further analysis. Written informed consent was obtained from all subjects and the protocol was approved by the medical ethical committee of the University Medical Center Utrecht.

Study Protocol

The use of gastric acid-inhibitory drugs and drugs that might influence gastrointestinal motility was discontinued 5 days before the study. Esophageal manometry was performed to determine the distance from nostrils to lower esophageal sphincter (LES). After this, the impedance and the pH catheter were introduced transnasally and positioned based on the manometric findings (see below).

The patients were instructed to press the event marker button on the pH datalogger whenever they experienced a symptom. The nature and time of onset of their symptoms had to be written down in a specially designed diary. Furthermore, they were instructed to consume three meals and two beverages with snack at fixed times during the 24-h measurement period. The period spent in supine position was also noted in the diary.

Esophageal Impedance and pH Monitoring

For intraluminal impedance monitoring a 7-channel impedance catheter (Aachen University of Technology, FEMU, Aachen, Germany) was used. This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2 cm long. The recording segments were located at 0–2, 2–4, 4–6, 8–10, 10–12, 14–16, and 17–19 cm above the upper border of the manometrically localized LES. Impedance signals were stored in a digital system (Aachen University of Technology) using a sample frequency of 50 Hz (11). Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and pH data were stored in a digital datalogger (Orion, MMS, Enschede, The Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH datalogger with the impedance datalogger the pH signals were also stored on the impedance datalogger ensuring synchronization.

Data Analysis

Analysis of the tracings was performed independently by two experienced investigators. The analysis was performed manually. Thereafter, the two investigators conjointly analyzed the reflux episodes that were not recognized by both of them. A consensus decision was made on each of these episodes. Signals recorded during consumption of meals and beverages were not taken into account during analysis of the data.

In the impedance tracings, gas reflux was defined as a rapid ($>$3,000 Ω/s) retrograde moving increase in impedance in at least two consecutive impedance sites (12). Liquid reflux was defined as a retrograde moving 40% fall in impedance in the two distal impedance sites (8). The pH tracings were analyzed for pH drops below 4. Furthermore, all pH drops $\geq$1 unit and drops $\geq$0.5 unit occurring within 5 s were identified. Drops $<$0.5 unit were judged to be not distinguishable from baseline noise, and were therefore not analyzed.

Using the combination of pH and impedance findings, 11 different definitions of reflux episodes were used, based on combinations of criteria such as the nature of the refluxate detected with impedance monitoring [liquid-containing (pure or mixed liquid) or gas], the magnitude of the pH drop (none, $\geq$0.5 unit, or $\geq$1.0 unit), and the nadir pH reached (acidic: pH $<$4; weakly acidic: pH 4–7) (Table 1). The reflux definitions listed in Table 1 fall into three broad categories: reflux episodes detected with pH-metry without use of impedance, liquid-containing reflux episodes (mixed liquid–gas and pure liquid) detected with impedance, and all reflux episodes detected with impedance (liquid-containing and pure gas).

Symptom–reflux association analysis was performed for each of the 11 definitions of reflux episodes listed in Table 1. A separate analysis was performed for weakly acidic reflux episodes, defined as liquid-containing reflux episodes with a nadir pH between 4 and 7, and the yields of symptom association analysis for acidic (pH $<$4), for weakly acidic reflux (pH 4–7) and for all reflux episodes pooled (independent of pH) were compared.

The first step in the symptom–reflux association analysis was the determination, for each reflux episode, whether it was symptomatic or not. Reflux episodes were labeled as symptomatic if a symptom occurred within the 2-min time window starting at the onset of the reflux episode (13). Only symptoms of heartburn and regurgitation were evaluated. Thereafter, the symptom index (SI), the symptom sensitivity index (SSI), and the symptom association probability (SAP) were calculated.

Table 1. The 11 Definitions of Reflux Episodes Distinguished in This Study

Reflux episodes identified by pH signal analysis
pH drop $<$4.0
pH drop $<$4.0 and/or pH fall $\geq$1.0 unit
pH drop $<$4.0 and/or pH fall $\geq$0.5 unit
Reflux episodes identified by impedance signal analysis
Liquid-containing reflux episodes (liquid and mixed gas/liquid)
with nadir pH $<$4.0
with nadir pH $<$4.0 and/or pH fall $\geq$1.0 unit
with nadir pH $<$4.0 and/or pH fall $\geq$0.5 unit
all (irrespective of pH)
Liquid-containing and pure gas reflux episodes
with nadir pH $<$4.0
with nadir pH $<$4.0 and/or pH fall $\geq$1.0 unit
with nadir pH $<$4.0 and/or pH fall $\geq$0.5 unit
all (irrespective of pH)

The SI was calculated according to Wiener *et al*. as the percentage of symptoms that was reflux related, *i.e.*, the percentage of symptom episodes that was preceded, within 2 min, by a reflux episode (14). The SSI was defined according to Breumelhof and Smout as the percentage of reflux episodes that was symptomatic, *i.e.*, the percentage of reflux episodes that was followed by a symptom within 2 min (15). The SAP was defined according to Weusten *et al*. as the statistical relation between symptoms and reflux episodes (16). The SAP is calculated by dividing the 24-h pH data set into consecutive 2-min segments. For each of these 2-min segments, it is determined whether reflux occurred in it, providing the total number of 2-min segments with and without reflux. Subsequently, it is determined whether or not a reflux episode occurred in the 2-min period before each symptom. A 2 × 2 table is then constructed in which the numbers of 2-min segments with and without symptoms and with and without reflux are tabulated. The Fisher exact test is used to calculate the probability (p) that the observed distribution was brought about by chance and that the symptom and reflux episodes were unrelated. The SAP is calculated as $(1-p) \times 100\%$. The cut-off values used in this study that quantify for a positive test were SI $\geq$50%, SSI $\geq$10%, and SAP $\geq$95%.

Statistical Analysis and Presentation of Data

Comparison of proportions of positive and negative SI, SSI, and SAP tests were performed using McNemar exact testing. Comparison of the proportion of patients with a positive SAP test for weakly acidic and acidic reflux calculated separately and calculated by pooling all reflux episodes was performed in a separate analysis. Differences were considered statistically significant when $p \leq 0.05$. Throughout the manuscript data are presented as mean ± SEM.

RESULTS

Of the 60 patients studied, 48 had at least one episode of heartburn or regurgitation during the 24-h study and the tracings of these patients were selected for further analysis. The mean number of reflux episodes that occurred during the 24-h study ranged from 42.5 ± 3.8 to 96.4 ± 6.4, depending on the definition of reflux (Table 2). As anticipated, more reflux episodes were identified with the impedance-based criteria than with the classical pH-based criterion (pH drop below 4). However, the classical pH drop definition not only led to false-negative but also to false-positive reflux detection (Fig. 1).

The proportion of patients with a positive SI varied between 45.8% and 62.5% and the proportion of patients with a positive SSI varied between 25.0% and 45.8%, depending on the definition of reflux episodes (Table 2). A positive SAP was found in 62.5–77.1% of the patients (Table 2). For liquid-containing reflux episodes, the highest proportion of patients with a positive SAP was reached with those episodes that were associated with a nadir pH <4 and/or a pH fall $\geq$0.5 unit (75.0%). For reflux episodes that showed evidence on impedance of liquid and/or gas reflux the highest number of cases with a positive SAP was found with episodes that had a nadir pH <4.0 and/or a pH fall $\geq$0.5 unit (77.1%). The difference between the highest proportion of positive SAP values obtained with impedance (77.1%) and without impedance monitoring (66.7%) was statistically significant ($p = 0.03$).

Only a minority of patients had a positive SAP for weakly acidic reflux (Table 3). Table 3 also shows the proportion of patients having a positive SAP for acidic, weakly acidic reflux, or a positive SAP for both (70.8% for liquid-containing reflux episodes and 72.9% for liquid-containing and gaseous reflux episodes). These proportions were not different from those found when the SAP was calculated independently of the pH of the reflux, *i.e.*, when all (acidic and weakly acidic) reflux episodes were pooled before calculation of the SAP.

DISCUSSION

Recent studies have suggested that impedance monitoring is helpful in the clinical evaluation of patients with proton pump inhibitor (PPI)-resistant symptoms, unexplained cough, excessive belching, and rumination (9, 17–20). It has been shown that symptoms of heartburn and regurgitation

Table 2. Number of Reflux Episodes (Mean ± SEM) and Subjects (%) with a Positive Symptom Association (SI, SSI, and SAP)

	Reflux Episodes	SI $\geq$ 50.0%	SSI $\geq$ 10.0%	SAP $\geq$ 95.0%
pH drop <4.0	48.6 ± 4.0	23 (47.9%)	20 (41.7%)	32 (66.7%)
pH drop <4.0 and/or fall $\geq$1.0 unit	67.6 ± 4.9	29 (60.4%)	16 (33.3%)	32 (66.7%)
pH drop <4.0 and/or fall $\geq$0.5 unit	96.4 ± 6.4	30 (62.5%)	12 (25.0%)	32 (66.7%)
Liquid-containing reflux with a nadir pH <4.0	42.5 ± 3.8	22 (45.8%)	22 (45.8%)	31 (64.6%)
Liquid-containing reflux with a nadir pH <4.0 and/or fall $\geq$1.0 unit	50.4 ± 4.1	28 (58.3%)	21 (43.8%)	34 (70.8%)
Liquid-containing reflux with a nadir pH <4.0 and/or fall $\geq$0.5 unit	55.3 ± 4.3	28 (58.3%)	22 (45.8%)	36 (75.0%)
All liquid-containing reflux episodes (independent of pH)	64.4 ± 4.4	28 (58.3%)	19 (39.6%)	35 (72.9%)
Liquid, mixed, and gas reflux with a nadir pH <4.0	47.5 ± 4.0	23 (47.9%)	20 (41.7%)	30 (62.5%)
Liquid, mixed, and gas reflux with a nadir pH <4.0 and/or fall $\geq$1.0 unit	55.2 ± 4.2	29 (60.4%)	19 (39.6%)	33 (68.8%)
Liquid, mixed, and gas reflux with a nadir pH <4.0 and/or fall $\geq$0.5 unit	62.1 ± 4.3	30 (62.5%)	19 (39.6%)	37 (77.1%)*
All liquid, mixed, and gas reflux episodes detected with impedance (independent of pH)	84.6 ± 5.1	30 (62.5%)	15 (31.3%)	36 (75.0%)

*$p < 0.05$ *vs* the highest SAP obtained without impedance monitoring.

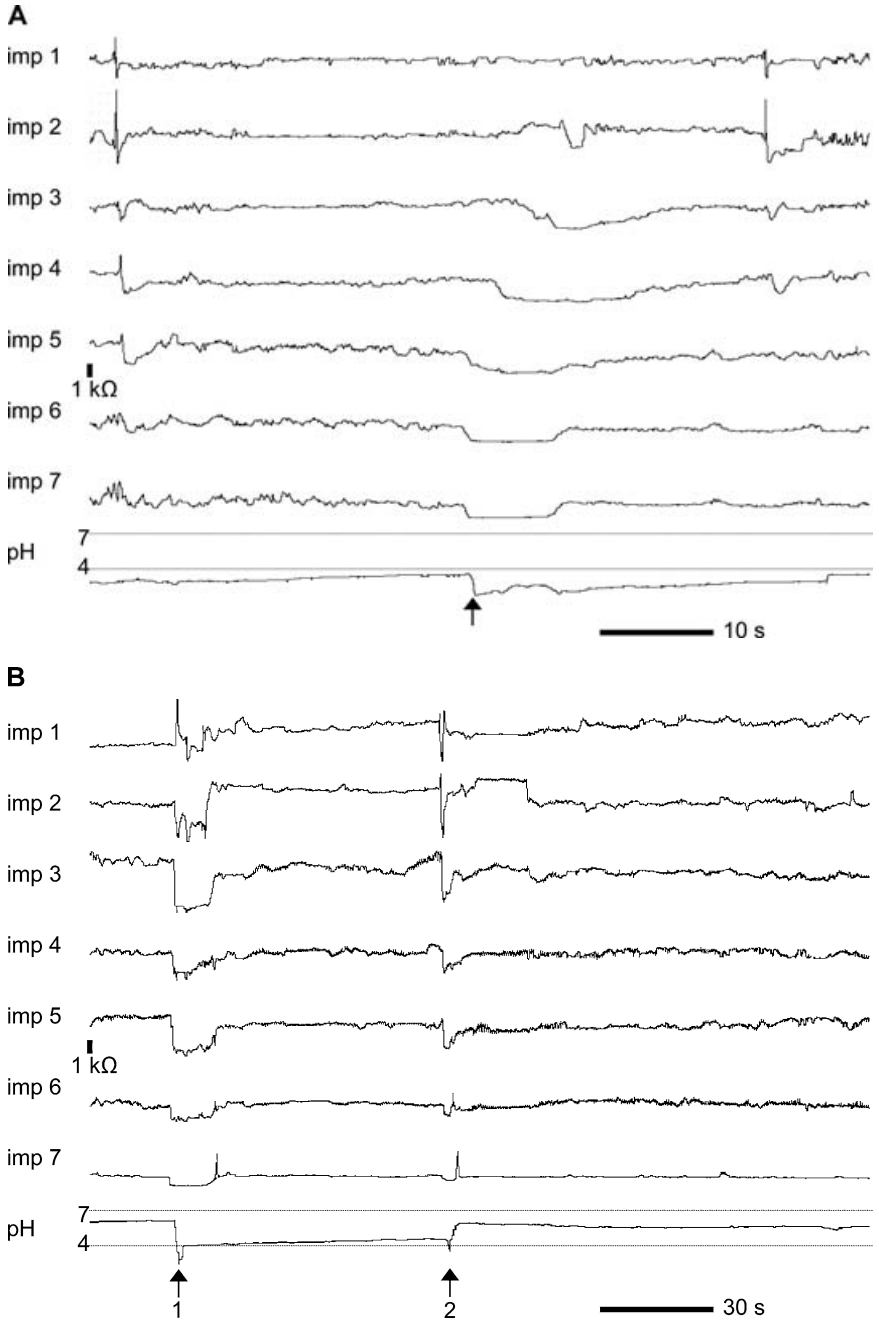

Figure 1. Examples of false-negative and false-positive detection of reflux episodes that may occur when the classical criterion of a pH drop below 4 is used, and that are unmasked by concomitant impedance monitoring. (*A*) In this example of false-negative detection, the "superimposed" reflux episode indicated by the arrow is not detected as such by classical pH criteria since the pH is still below 4 as the consequence of a preceding reflux event (not shown). (*B*) In this example of false-positive detection, the second drop in pH passing the pH 4 threshold (2) is not caused by reflux but by a swallow (antegradely propagated impedance drop).

can be induced by weakly acidic reflux but it remained unknown whether the use of impedance monitoring results in identification of a larger proportion of patients whose symptoms are induced by gastroesophageal reflux. In this study, we have used three different methods for reflux–symptom association analysis, *i.e.*, the SI, SSI, and SAP. The SI and SSI are relatively simple indices, representing the percentage of symptom episodes that is preceded by reflux (SI) and the percentage of reflux episodes that is followed by a symptom (SSI). The major shortcoming of the SI is that it does not take the total number of reflux episodes into account. The higher the number of reflux episodes, the higher the chance that a symptom occurs within 2 min after a reflux episode by coincidence. Likewise, the SSI fails to take the number of symptom episodes into account, and a high number of symptom episodes is likely to result in a high index. The advantage

Table 3. Number of Subjects (%) with a Positive SAP for Acid and Weakly Acidic Reflux Separately, a Positive SAP for at Least One of These Two Reflux Types and a Positive SAP as Calculated from All Reflux Episodes Independent of pH

	Acid (Nadir pH <4)	Weakly Acidic (Nadir pH 4–7)	Acid and/or Weakly Acidic Reflux	All Reflux Episodes (Independent of pH)
Liquid-containing reflux episodes	31 (64.6%)	10 (20.8%)	34 (70.8%)	35 (72.9%)
Liquid-containing and pure gas reflux episodes	30 (62.5%)	8 (16.7%)	35 (72.9%)	36 (75.0%)

of the SAP is that it takes all relevant factors into account, but its disadvantage is that this parameter is difficult to calculate manually.

Theoretically, incorporation of weakly acidic reflux episodes into reflux–symptom association analysis will have different effects on the three indices (SI, SSI, and SAP). Since the SI is defined as the percentage of reflux-induced symptoms with the total number of symptoms as the denominator, this index will most likely increase by incorporation of weakly acidic reflux episodes. In contrast, the SSI is likely to decrease with the incorporation of more reflux episodes as this index is defined as the percentage of reflux-related symptoms, with the total number of reflux episodes as the denominator. Because of the complexity of the calculations involved, the effect of incorporation of a higher number of reflux episodes on the value of the SAP cannot be predicted easily.

A recent study of Taghavi *et al*. compared the predictive value for GERD of the different symptom indices with as a gold standard for GERD the response to a short-term treatment with omeprazole, the PPI test (21). While these authors found relatively high positive predictive values for the SI, SSI, and SAP, the negative predictive values of the indices were relatively low. However, the PPI test is far from ideal as a gold standard, as other conditions such as functional dyspepsia and peptic ulcer disease may also respond favorably to treatment with omeprazole (22). It is therefore not surprising that the negative predictive values of the symptom association parameters were found to be relatively low.

This study has shown that reflux episodes defined on the basis of impedance parameters provide a consistently higher SI and SAP than reflux episodes defined on the basis of pH changes only. This results in identification of a larger proportion of patients in whom reflux is the likely cause of their symptoms. In particular, small increases in the SAP, induced by incorporation of impedance monitoring, from, for example, 87% to 97% will change the patient's diagnosis (threshold 95%) and might have therapeutic implications.

It has been shown that a positive SAP for acid reflux, detected with pH-metry, predicts the outcome of medical and surgical therapy for GERD (21, 23). However, this has not yet been investigated for a positive SAP for reflux detected with impedance, which includes acidic and weakly acidic reflux. It is thus uncertain whether investigation of patients using combined impedance-pH monitoring leads to a better selection for treatment. Furthermore, it is uncertain whether symptoms due to weakly acidic reflux episodes will respond to acid-suppressive therapy.

In some studies, separate symptom association analysis was performed for acid and weakly acidic reflux. In our study, we show such a procedure does not result in the identification of a higher proportion of patients with reflux-related symptoms than a symptom analysis in which all reflux episodes are pooled before the relation between reflux episodes and symptoms is tested. A theoretical rationale for dividing reflux episodes into acid and weakly acidic reflux episodes could be that some patients have predominantly acid reflux while others have predominantly weakly acidic reflux, but this does not seem to be the case. Another rationale would prevail if the treatment would be different for these two types of reflux, but currently both are treated with anti-secretory therapy since drugs that reduce the incidence of reflux episodes, such as GABA-B receptor agonists, are still under development (24). Furthermore, no strict distinction can be made by the symptoms associated with acid and weakly acidic reflux, as heartburn and regurgitation can be produced by reflux episodes with various pH values (10). Future research will determine whether classification of reflux episodes into acidic and weakly acidic remains useful or that it is only a historical remnant of the era in which esophageal pH monitoring was the only available technique for quantification of gastroesophageal reflux. Most symptomatic weakly acidic reflux episodes are associated with a small but noticeable drop in pH. This suggests that hypersensitivity to acid plays an important role in the generation of symptoms by weakly acidic reflux episodes, but other factors, such as the presence of pepsin in the refluxate and esophageal distention by the refluxate, are also likely to play a role (10, 25).

The number of symptoms experienced by patients with GERD is dependent on both the sensitivity to acid of the patient's esophagus and the total number of reflux episodes. Patients with a pronounced esophageal hypersensitivity but a normal esophageal acid exposure may experience heartburn after reflux episodes that induce only small changes in pH (26). When reflux definitions with stringent criteria for reflux episodes are used, patients are likely to have a number of symptoms not related to reflux (defined by these criteria) and thus have a low SAP score. For example, when the definition for reflux episodes used is "liquid-containing reflux episodes with a nadir pH <4," all symptoms that follow a weakly acidic reflux episode (pH 4–7) are classified as not reflux-related and these will lower the SAP score. Incorporating more criteria into the definition of reflux (*e.g.*, inclusion of pH falls of more than 0.5 unit) will result in identification of more patients with a hypersensitivity to acid. In our study, widening the criteria

for reflux from liquid reflux episodes with a nadir pH <4 (acid reflux) to all liquid reflux episodes (acid and weakly acidic) changed the SAP from a negative to a positive score in 4 of the 48 patients (Table 2). Of these four patients, three had a physiological acid exposure and the mean acid exposure time of the four patients was 3.1%. Identification of these patients is important since it is likely that they will respond favorably to high-dose proton pump inhibiting therapy. It has been shown that in a group of patients with symptoms of heartburn and regurgitation and a physiological esophageal acid exposure, those with a positive SI have a better response to omeprazole (27).

The proportion of patients with a positive SAP score for the various reflux definitions varied between 62.5% and 77.1%. This implies that the majority of these patients have a positive association between reflux and symptoms. The fact that the patients in this study were selected by experienced gastroenterologists and that our tertiary care clinic is specialized in motility disorders might account for the high yield of symptom association analysis in this study. Furthermore, the instruction of the patients before the 24-h measurement was performed meticulously.

In this study, we found that approximately one third of the reflux episodes defined as pH drop to below 4 and/or pH drop $\geq$0.5 unit (96.4 $\pm$ 6.4) is not accompanied by evidence of reflux on impedance (62.1 $\pm$ 4.3). An example of this phenomenon is displayed in Figure 1. In previous studies, reflux detected with pH-metry only was rare (28, 29). However, in those studies, reflux was defined as a pH drop <4.0. Preliminary data from Hila *et al*. suggested that small pH drops are not accurate for reflux detection, as they were often not associated with evidence of reflux on impedance but occurred during swallowing (30). It is uncertain whether these pH drops are indeed not good indicators of reflux or that these pH drops indicate reflux episodes that are missed by impedance because they occur during swallows. It is well known that during swallow-induced LES relaxation reflux often occurs (31).

In conclusion, although reflux–symptom association analysis based on pH-metric data can identify reflux as the source of heartburn and regurgitation in the majority of patients, addition of impedance monitoring leads to identification of a significantly higher proportion of patients who suffer from reflux-induced symptoms. Thus, impedance monitoring has an additional value for the evaluation of heartburn and regurgitation in patients off PPI therapy. Performing separate symptom association analysis for acidic and weakly acidic reflux episodes does not result in a higher yield than performing symptom association analysis for all reflux episodes pooled.

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STUDY HIGHLIGHTS

What is Current Knowledge

- Symptom association analysis of 24-hr pH-metry is the current gold standard to determine whether a patient's symptoms are due to gastroesophageal reflux.
- With pH-metry only acid reflux episodes (pH drop below 4) can be detected while weakly acidic reflux episodes (pH between 4 and 7) may also elicit symptoms.
- Esophageal impedance monitoring can detect both acidic and weakly acidic reflux episodes.

What is New Here

- Combined pH-impedance monitoring finds more patients (off therapy) who are suffering from reflux-induced symptoms than pH-metry alone.

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