ALIMENTARY TRACT

Normal Values of Pharyngeal and Esophageal 24-Hour pH Impedance in Individuals on and off Therapy and Interobserver Reproducibility

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BACKGROUND & AIMS: Combined pH and impedance monitoring can detect all types of reflux episodes within the esophageal lumen and the pharynx. We performed a multicenter study to establish normal values of pharyngeal and esophageal pH-impedance monitoring in individuals on and off therapy and to determine the interobserver reproducibility of this technique.

METHODS: We collected ambulatory 24-hour pH-impedance recordings from 46 healthy subjects by using a bifurcated probe that allowed for detection of reflux events in the distal and proximal esophagus and pharynx. Data were collected when subjects had not received any medicine (off therapy) and after receiving 40 mg esomeprazole twice daily for 14 days (on therapy). The interobserver agreement for the detection of reflux events was determined in 20 subjects off and on therapy. Results were expressed as median (interquartile range).

RESULTS: Off therapy, subjects had a median of 32 reflux events (17–45) in the distal esophagus and 3 (1–6) in the proximal esophagus; they had none in the pharynx. On therapy, subjects had a median number of 21 reflux events (6–37) in the distal esophagus and 2 (0–5) in the proximal esophagus; again, there were none in the pharynx. Interobserver agreement was good for esophageal reflux events but poor for pharyngeal events.

CONCLUSIONS: We determined normal values of pharyngeal and gastroesophageal reflux events by 24-hour pH-impedance monitoring of subjects receiving or not receiving esomeprazole therapy. Analyses of esophageal events were reproducible, but analyses of pharyngeal events were not; this limitation should be taken into account in further studies. Eudract.ema.europa.eu, Number: 2010-022845-48.

Multichannel intraluminal esophageal impedance monitoring allows ambulatory detection of all types of gastroesophageal reflux (GER) events as well as assessment of their proximal extent within the esophagus. Combined pH-impedance monitoring allows characterization of reflux episodes as acid, weakly acidic, or weakly alkaline and has been considered as the best tool to detect and characterize GER by a panel of experts.[1] To date, several sets of normal values for GER events have been reported, all of them being obtained off proton pump inhibitor (PPI) therapy.[2,3] However, in patients off PPIs, the added value of pH-impedance compared with pH-alone studies is limited,[4] and most pH-impedance recordings are performed in patients on antisecretory drugs. As a consequence,

there is a need for a full data set of normal values of 24-hour pH-impedance monitoring on PPIs twice daily,[5] because only a short series (n = 20) has been reported so far.[6] Finally, to the best of our knowledge, no interobserver reproducibility data are available in the literature for the detection of distal and prox-

imal GER events, despite the introduction of pH-impedance monitoring more than 10 years ago.

The impedance technology has been recently used to detect reflux events reaching the pharynx. Indeed, pH alone recordings in the proximal esophagus and/or in the pharynx have several limitations: (1) inaccurate and not reproducible catheter position, (2) drops in pH values attributed to artifacts because of the absence of any corresponding decrease in the distal esophageal pH, (3) controversies about normal values, and (4) the inability of conventional pH probes to detect gaseous and/or weakly acidic reflux.[7] Considering that, pharyngeal impedance catheters have been developed. They consist of bifurcated catheters allowing reliable positioning of the impedance and pH sensors above the upper and lower esophageal sphincters, whatever the height of the subject. In a short series of patients with gastroesophageal reflux disease (GERD) and controls, Kawamura et al[8] observed that reflux into the pharynx was very uncommon, whereas Oelschlager et al[9] have reported a median number of 5 pharyngeal reflux (PR) episodes in 10 asymptomatic controls. More recently, Hoppo et al[10] reported only 1 PR event in 34 healthy subjects off PPIs and 4 events in 2 of 25 subjects on PPIs. These discrepancies clearly demonstrate that analysis of pharyngeal impedance tracings is challenging and requires accurate and reproducible diagnostic criteria before this technique may find some applications in clinical practice.

The aims of this multicenter study were (1) to establish normal values of PR and GER by using pharyngoesophageal 24-hour pH-impedance monitoring off and on PPI therapy and (2) to determine the interobserver reproducibility for the analysis of these recordings.

Study Design and Subjects

Subjects

Healthy volunteers were recruited by advertising in 6 University Hospitals in France (Bordeaux, Nantes, Lyon, Rouen, Colombes, and Rennes). A careful interview was conducted to exclude the presence of typical (heartburn, regurgitation) and atypical symptoms (increased belching, cough, asthma or wheezing, hoarseness, chest pain) suggestive of or potentially related to GERD. Exclusion criteria were history of thoracic or digestive surgery (except appendectomy), alcohol consumption >40 g/d, smoking >10 cigarettes/day, nursing mothers, subjects on medications that alter intragastric acidity or esophageal motility, as well as those with history of diabetes, neurologic disorder, gastrointestinal disease, and allergy to esomeprazole or benzimidazole derivates. Concomitant treatment with clopidogrel was prohibited. Written informed consent was obtained from all subjects, and the protocol was approved by the Comité de Protection des Personnes Sud-Ouest Outre-Mer 3. The subjects received financial compensation for their participation in the study.

Study Protocol

The studies were performed on an outpatient basis after an overnight fast. Upper esophageal sphincter (UES) and esophagogastric junction (EGJ) were first located by using high-resolution esophageal manometry. Studies were performed with a bifurcated pH-impedance catheter (Sandhill Scientific, Inc, Highlands Ranch, CO) (Figure 1). The long arm branch of the catheter had 2 electrode pairs positioned at 3 and 5 cm proxi-

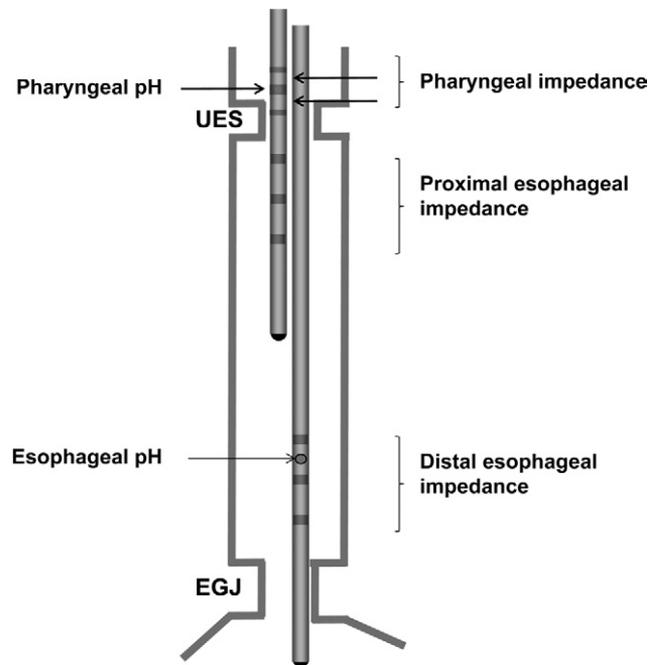
Figure 1. Bifurcated esophageal and pharyngeal pH-impedance catheter. The long arm branch has 2 impedance electrode pairs positioned 3 and 5 cm above the EGJ and a pH sensor positioned 5 cm above the EGJ. The short arm branch has 4 impedance electrode pairs positioned 2 and 4 cm below the UES and 0 and 1 cm above the UES; a pH sensor is located 0.5 cm above the UES.

mal to the EGJ, with a pH sensor positioned 5 cm proximal to the junction. The short arm branch had 2 electrode pairs in the proximal esophagus and 2 pairs in the hypopharynx, with a second pH sensor located 0.5 cm proximal to the upper border of the UES. Before recording, the catheter was calibrated by using pH 4.0 and pH 7.0 buffer solutions. An external reference electrode was attached to the anterior chest wall over the midsternum. The long branch of the catheter was placed transnasally to have the esophageal pH sensor located 5 cm proximal to the EGJ. The short branch of the catheter was then placed to have the pharyngeal pH sensor 0.5–1 cm above the upper limit of the UES. Subjects were encouraged to maintain their normal activities and sleep schedule and eat their usual meals. After the first recording, subjects received esomeprazole 40 mg twice a day before breakfast and evening meals for 2 weeks. Then, a second pH-impedance recording on PPIs twice daily was performed according to a similar protocol. The catheters were placed at the same level as during the first recording. Subjects were instructed to reproduce as far as possible similar levels of activity and food intake between the first and second recordings.

Data Analysis

Tracings were visually analyzed by using assistance of the Bioview Analysis software (version 5.6.0.0; Sandhill Scientific, Inc). Meals were excluded for the analysis. GER and PR events were defined as follows.

For GER events, liquid reflux was defined as a retrograde 50% drop in impedance starting distally (at the level of the EGJ) and propagating to at least the next 2 more proximal impedance
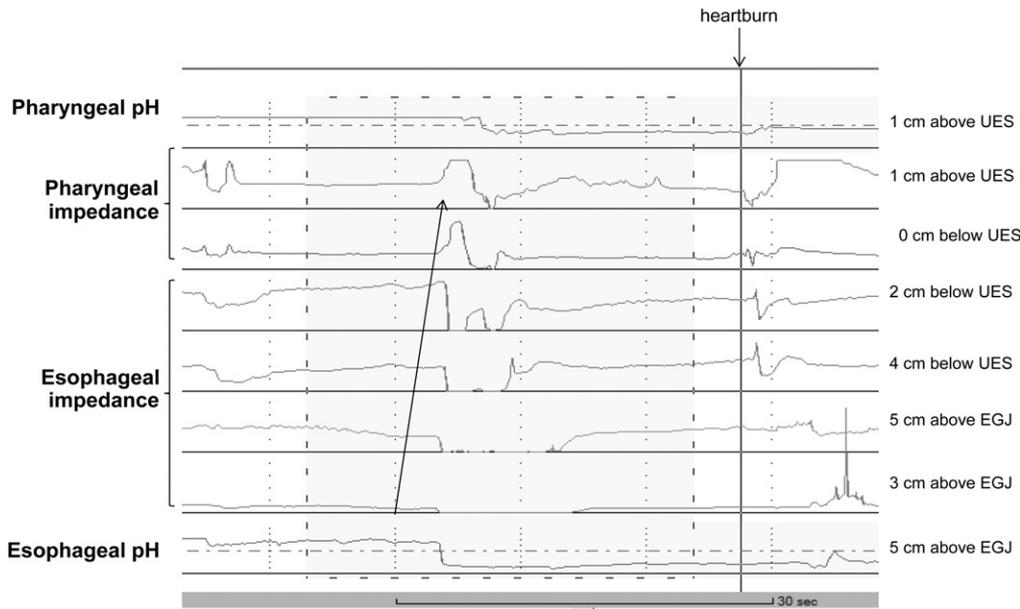
Figure 2. Example of GER and PR events in a patient with heartburn and sore throat. Channels location related to EGJ or UES is indicated on the right. There is a drop in impedance starting distally (at the level of the EGJ) and reaching the more proximal pharyngeal impedance site. GER as well as PR events are acid (pH drops below 4). The *vertical line* corresponds to a heartburn episode.

measuring segments. Gas reflux was defined as a rapid (3 kΩ/s) increase in impedance >5000 Ω, occurring simultaneously in at least 2 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. Pure gas reflux events (belches without liquid component) were not taken into account. Liquid or mixed reflux episodes were characterized by pH as acid, weakly acidic, or weakly alkaline[1]: (1) acid reflux, reflux event associated with a drop of esophageal pH below 4; (2) weakly acidic reflux, reflux events associated with an esophageal pH between 4 and 7; and (3) weakly alkaline reflux, reflux event during which nadir esophageal pH does not drop below 7. The following parameters were obtained: bolus exposure (reflux percent time), median bolus clearance time (seconds), esophageal acid exposure (%), and mean acid clearance time (seconds). Reflux events were considered as proximal if the impedance drop reached the impedance site located 4 cm below the UES.

PR event was defined as a retrograde 50% drop in impedance starting distally (at the level of the EGJ) and reaching the more proximal pharyngeal impedance site. Pharyngeal events were characterized as acidic, weakly acidic, or weakly alkaline according to the minimal pharyngeal pH value during the impedance drop. PR event was considered only if it was preceded by retrograde impedance drop both distally and proximally within the esophagus and if no swallow occurred during the pharyngeal impedance drop. Careful attention was taken to the baseline value regarding the frequent artifacts in impedance values within the pharynx, especially when trapped air was present. For this reason, gaseous PR events were not analyzed. An example of PR event is shown in Figure 2.

All the tracings were further carefully reviewed by 2 experts (F.Z. and S.R.). Therefore, the final data presented are the results of this consensus analysis.

Interobserver agreement was specifically assessed on a subset of 38 pH-impedance studies (20 off PPI and 18 on PPI) from 20 subjects. The tracings were first reviewed independently by the 2 experts and then reviewed by both observers to obtain a consensus.

Statistical Analysis

Data are expressed as median and percentile values (25th, 75th, and 95th percentiles). Paired Student t test was used for comparison between off and on PPI values. An error probability of $P \leq .05$ was considered statistically significant.

For interobserver reproducibility assessment, the number of proximal and distal GER and PR events detected per tracing independently by each observer and by the consensus were noted and compared by using paired t test.

For each recording, the following parameters were calculated by using the consensus review as a gold standard: percentage of reflux events correctly diagnosed by both reviewers and percentage of reflux events missed and misdiagnosed as reflux. The percentage of reflux events detected by each observer was compared by using paired t test as well as the percentage of reflux correctly diagnosed as reflux by each observer. Finally, a percentage of concordance between the 2 observers was calculated as (Number of reflux events detected independently by both observers/Number of events detected by at least one observer) × 100.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Subjects

Fifty-six healthy subjects were included; 3 withdrew their consent before the first pH-impedance recording, and 7 were further excluded because of a wrong placement of the catheters (inversion of long and short branch in one center). No subject had significant esophageal motor disorder on manometry.

Off PPI recordings were available in 46 subjects (22 women; mean age, 46.3 years; range, 18–78 years; mean body mass index, 23.9 kg/m²; range, 16.4–31.8). Age was distributed as follows: 10 subjects between 18 and 30 years, 15 between 30 and 50 years, 14 between 50 and 60 years, and 7 older than 60 years. Recordings on PPI were available in 40 subjects (19 women;

Table 1. Parameters of GER off and on PPI

	Off PPI (n = 46)		On PPI (n = 40)		
	Median (IQR)	95th percentile	Median (IQR)	95th percentile	P value
All GER events (n)	32 (17–45)	53	21 (6–37)	57	<.002
Upright	28 (13–42)	51	19 (6–34)	55	<.002
Supine	2 (1–3)	7	0 (0–2)	8	NS
Acid GER events (n)	22 (9–35)	40	0 (0–1)	7	<.001
Upright	20 (8–33)	39	0 (0–1)	5	<.001
Supine	1 (0–2)	6	0 (0–0)	1	<.001
Weakly acidic GER events (n)	8 (3–12)	21	21 (6–35)	55	<.001
Upright	7 (3–11)	21	20 (6–33)	45	<.001
Supine	0 (0–1)	4	0(0–1)	7	NS
Weakly alkaline GER events (n)	0 (0–0)	0	0 (0–0)	2	NS
Upright	0 (0–0)	0	0 (0–0)	2	NS
Supine	0 (0–0)	0	0 (0–0)	0	NS
Proximal reflux event (n)	3 (1–6)	10	2 (0–5)	9	<.002
Esophageal acid exposure (%)	1.5 (0.4–2.6)	5.8	0.0 (0.0–0.0)	0.4	<.001
Upright	1.8 (0.5–3.9)	6.7	0.0 (0.0–0.0)	0.1	<.001
Supine	0.1 (0.0–0.3)	6.8	0.0 (0.0–0.0)	0.0	<.05
Esophageal bolus exposure (%)	1.0 (0.5–1.5)	2.3	0.6 (0.1–0.9)	2.1	<.002
Upright	1.4 (0.8–2.2)	4.2	1.0 (0.2–1.3)	3.2	<.003
Supine	0.1 (0.0–0.2)	1.6	0.0 (0.0–0.1)	0.2	NS
Mean acid clearance time (*sec*)	62 (41–103)	197	22 (14–35)	88	<.001
Median bolus clearance time (*sec*)	16 (13–21)	46	15 (9–21)	35	NS

NOTE. Drug dosage is esomeprazole 40 mg twice a day for 2 weeks.
IQR, interquartile range.

mean age, 47.5 years; range, 18–78), because 6 were further excluded for technical issues (artifacts with high impedance levels throughout the whole recording, n = 4; recording duration less than 20 hours, n = 2).

Gastroesophageal Reflux

Off and on PPI GER parameters are summarized in Table 1. PPI therapy significantly decreased the number of GER events (*P* < .002), although the 95th percentile values were similar off and on therapy (53 and 57, respectively). PPI therapy induced a change in the chemical content of the refluxate, with a significant decrease of acid GER events (*P* < .001) and a concomitant increase of weakly acidic GER events (*P* < .001). There was virtually no weakly

alkaline reflux event off as well as on therapy. PPI therapy also significantly decreased the number of proximal GER events (*P* < .002), esophageal acid exposure (*P* < .001), esophageal bolus exposure (*P* < .002), and mean acid clearance time (*P* < .001). At the opposite, median bolus clearance time was not significantly different on and off therapy.

Pharyngeal Reflux

PR parameters off and on PPIs are shown in Table 2. A total of 32 PR events were detected in 12 subjects off therapy. One subject had 12 PR events, including 11 acidic PR, all in the upright position. This subject did not have any evidence of pathologic distal GER (total acid exposure, 2.3%) but had an

Table 2. Parameters of PR off and on PPIs

	Off PPI (n = 46)		On PPI (n = 40)		
	Median (IQR)	95th percentile	Median (IQR)	95th percentile	P value
PR events (n)	0 (0–0)	3	0 (0–0)	1	<.02
Upright	0 (0–0)	2	0 (0–0)	1	<.03
Supine	0 (0–0)	0	0 (0–0)	0	NS
Acid PR events (n)	0 (0–0)	2	0 (0–0)	0	.05
Weakly acidic PR events (n)	0 (0–0)	1	0 (0–0)	1	<.03
Weakly alkaline PR events (n)	0 (0–0)	0	0 (0–0)	0	NS
Liquid PR events (n)	0 (0–0)	1	0 (0–0)	0	NS
Mixed PR events (n)	0 (0–0)	3	0 (0–0)	0	<.02
Pharyngeal acid exposure (%)	0.0 (0.0–0.0)	0.0	0.0 (0.0–0.0)	0.0	NS
Pharyngeal bolus exposure (%)	0.0 (0.0–0.0)	0.0	0.0 (0.0–0.0)	0.0	<.04
Median pharyngeal bolus clearance time (*sec*)	1 (0–3)	12	10 (1–19)	31	NS

NOTE. Drug dosage is esomeprazole 40 mg twice a day for 2 weeks.
IQR, interquartile range.

Table 3. Percentages of Distal and Proximal GER Events Detected per Subject by Each Observer and by Both Observers

	% Events detected by both observers	% Missed events		% Misdiagnosed events	
		Observer 1	Observer 2	Observer 1	Observer 2
Off PPIs					
Distal GER events	87 (83–92)	4 (0–6)	7 (4–10)	0 (0–5)	0 (0–7)
Proximal GER events	68 (53–86)	0 (0–2)[a]	26 (0–35)	28 (10–42)	0 (0–28)
On PPIs					
Distal GER events	82 (72–90)	8 (6–11)	7 (0–17)	5 (0–7)	7 (0–13)
Proximal GER events	62 (50–100)	0 (0–0)	33 (3–50)	9 (0–42)	0 (0–33)

NOTE. Data are expressed as median (interquartile range).

[a]$P < .05$ vs observer 2.

abnormally high number of proximal GER events (n = 27). Overall, the median number of PR events off therapy was 0 (0–0), with a 95th percentile value of 3. Excluding the subject with 12 PR events did not change these values. Most PR events occurred in upright position ($P < .03$ vs supine position). There were 19 acid PR events vs 13 weakly acidic PR events (NS); 18 PR events were mixed, and 14 were pure liquid (NS). Regarding the low number of PR events, both pharyngeal acid and bolus exposures were very low (median values, 0 [0–0]).

PPI therapy significantly reduced the number of PR events from 32 to 4 events observed in 4 of 40 subjects ($P < .02$). The 95th percentile for the total number of PR events on PPI was 1. PPIs also significantly decreased the number of acid, weakly acidic, and mixed PR events as well as pharyngeal bolus exposure. The 4 PR events on PPIs occurred in the upright position and were weakly acidic. Two were pure liquid, and 2 were mixed. Of note, the subject with 12 PR events off therapy had only 1 weakly acidic PR on PPIs.

Interobserver Reproducibility

The number of events detected by each observer was not statistically different except for proximal events off PPIs (data not shown). The majority of distal events were detected by both observers, and approximately two-thirds of proximal events were identified by both observers. The overall concordance between the 2 observers was 84% and 73% for the detection of distal events off and on PPIs, respectively, and 50% and 42%, respectively, for proximal events. As shown in Table 3, the disagreement between the 2 observers was due to missed events as well as misdiagnosed events.

Eleven PR events were diagnosed off PPI by the consensus review in 6 subjects, whereas observer 1 detected 18 PR events in 8 subjects and observer 2 only 7 events in 6 subjects. Only 1 event was diagnosed as PR by both observers. Among the 14 subjects without PR according to the consensus review, only 9 were diagnosed without PR events by both observers.

On PPI, only 1 PR was identified by the consensus review (vs 3 for observer 1 and 4 for observer 2). None of the events were detected by both observers. Among the 17 subjects without PR, 14 were correctly diagnosed by both observers.

Discussion

This pH-impedance study provides a full data set of normal values for GER and PR off and on PPIs, together with interobserver reproducibility data. It is important to note that these data have been obtained after a careful review of each

tracing by 2 experts in the field of pH-impedance monitoring. Therefore, to be taken into account in the final data set, each individual reflux event had to be confirmed by the 2 experts. Moreover, efforts were made to have a population of healthy subjects that could be considered as the most representative as possible. Indeed, not only the mean age was 46.3 years, but 21 of 46 subjects were older than 50, including 7 older than 60.

Regarding GER data obtained off therapy, the numbers of GER events appear to be lower than those previously published by our group.[3] As an example, the total number of GER events expressed as median was 32 vs 44 in our previous series. These discrepancies may be related to the use of a bifurcated catheter or to the smaller size of the series (46 subjects vs 72) as well as an older age of the subjects (46.3 vs 35 years), although we have previously shown that age did not influence the number of GER events in healthy subjects.[3] Most likely, the method of analysis may have played a crucial role to explain these discrepancies. We did not perform any consensus review in the previous study, and it is very likely that a lot of discrepancies occurred in tracings analysis between centers. This hypothesis is supported by the fact that esophageal acid exposure values (which are not influenced by manual analysis) were very similar in both series. This is the reason why data on interobserver reproducibility are very relevant. The agreement between the 2 experts involved in the present study was better for distal GER events (84% and 73% off and on PPIs, respectively) than for proximal GER events (50% and 42%, respectively). The main reason for discrepancies was a different interpretation of impedance drop within the proximal esophagus, which is considered either as related to a swallow or as a retrograde flow of liquid. Thus, these data confirm that visual analysis of impedance tracings is challenging and requires time and experience.

We present here a full data set of normal values for GER events on PPIs twice daily. In contradiction with previous results obtained in GERD patients,[11,12] we observed in healthy subjects that PPI therapy not only changed the chemical composition of the refluxate but also significantly reduced the total number of distal and proximal GER events. Mean acid clearance time and esophageal acid and bolus exposures also decreased on PPI. These results are very similar to those previously reported in an abstract form in a shorter series of healthy subjects (n = 20).[6] These effects are probably related to decreased volume of gastric secretion and thereby of gastric contents available for GER.[13] The esophageal acid exposure on esomeprazole 40 mg twice a day is lower (median, 0 [0–0, 0.4%]) than previously reported with omeprazole 40 mg daily (cutoff value of 1.6%).[14] These differences are likely related to the lower dose of PPIs in the previous study.
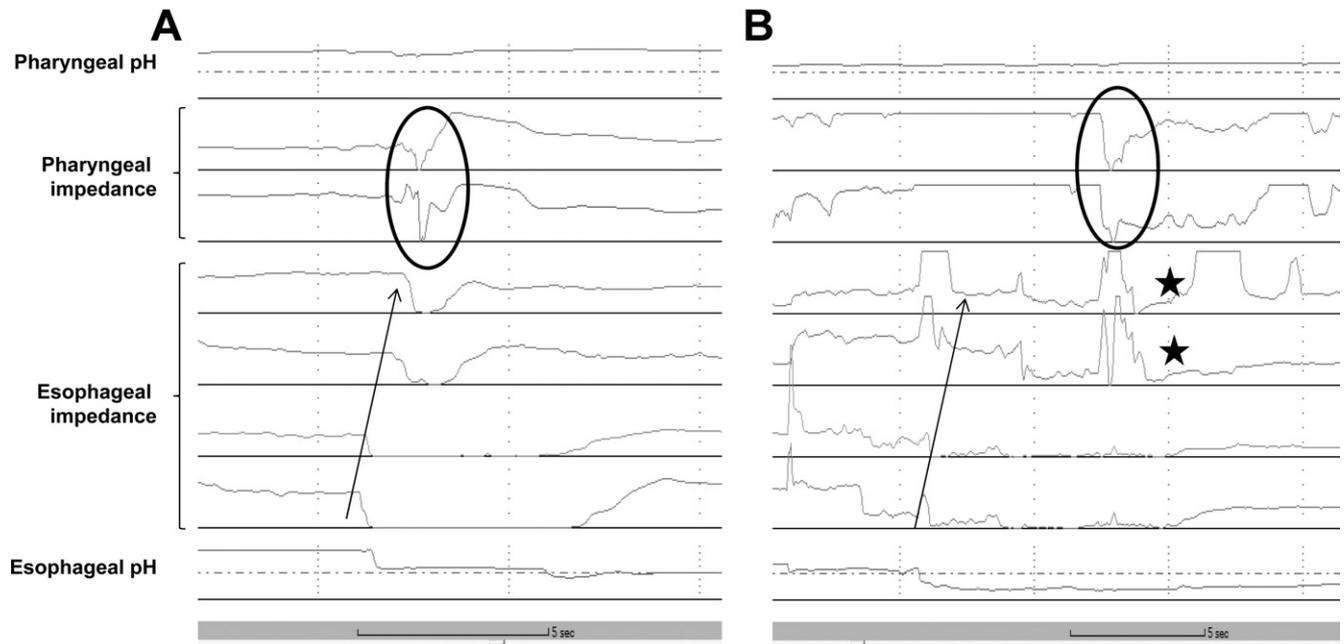
Figure 3. Examples of difficult analysis of pharyngeal impedance signals. (*A*) Liquid acid GER episode (*arrow*) with high proximal extent. After changing the time scale, the impedance drop in the pharyngeal channels was considered as a swallow. (*B*) Mixed acid GER event with high proximal extent and an impedance drop in the 2 pharyngeal channels initially considered as a swallow (*black stars*). After changing the time scale, this was considered as a PR.

Similar to previous studies,[8,10] we confirm that esophagopharyngeal reflux is a rare event in asymptomatic subjects. We report the same median number of PR events as Hoppo et al,[10] who included 34 subjects, ie, 0 (0–0) in subjects off therapy. However, we detected many more PR events, ie, 32 in 46 subjects vs only 1 in 34 subjects, and as a consequence, the 95th percentile value is 3 in our series vs 0 in the study by Hoppo et al. The reasons for these discrepancies might be explained by the consensus review performed in our study, whereas this is not mentioned in the study by Hoppo et al. Regarding our poor interobserver agreement, we considered that a consensus review was mandatory. We initially defined stringent diagnostic criteria for PR event considered only if preceded by retrograde drop in impedance distally and proximally within the esophagus and if no swallow occurred during the drop in pharyngeal impedance. This stringent definition was not sufficient to reach good levels of interobserver agreement because only 1 event was initially diagnosed by both observers among the 11 PR events diagnosed off therapy by the consensus review. The main issue with pharyngeal signals is to differentiate an actual retrograde drop in impedance from a swallow, as illustrated by Figure 3. Moreover, pharyngeal impedance values are often very high and artifacted, reflecting the presence of air within the hypopharynx and making it difficult to define the baseline values. This is the reason why we consider that impedance is not adequate for the detection of pure gas PR. Esomeprazole 40 mg twice daily resulted in a significant decrease in PR events that were all of weakly acidic composition. As for the study by Hoppo et al, the upper limit of normal for PR events on PPIs twice daily in our series is 1. This value may be important to consider because most patients with suspected reflux-related pharyngolaryngeal symptoms will be studied on therapy.

In conclusion, the present data will help to determine the relevance of findings in patients with suspected laryngopharyngeal reflux associated or not with typical GERD symptoms. Whether pharyngeal impedance monitoring has promise in the management of these patients requires further outcome studies. Indeed, analysis of pharyngeal signals is difficult and poorly reproducible and should take into account distal and proximal esophageal events. These limitations justify a rigorous consensus review in further clinical studies.

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Reprint requests

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