

Pharyngeal pH monitoring better predicts a successful outcome for extraesophageal reflux symptoms after antireflux surgery

Stephanie G. Worrell · Steven R. DeMeester ·
Christina L. Greene · Daniel S. Oh ·
Jeffrey A. Hagen

Received: 26 April 2013 / Accepted: 14 June 2013
© Springer Science+Business Media New York 2013

Abstract

Background Gastroesophageal reflux disease can be associated with extraesophageal symptoms (hoarseness, cough, asthma, and globus). However, these symptoms may have a multifactorial etiology. Proximal pH monitoring has been proposed as a means of identifying patients where reflux is the cause of the extraesophageal symptoms. The aim of this study was to determine whether proximal esophageal or pharyngeal pH monitoring better identified patients with extraesophageal symptoms that improved after antireflux surgery.

Methods A retrospective chart review was performed to identify all patients who had esophageal and pharyngeal pH monitoring before an antireflux operation. A composite score was used to define an abnormal result with each test. A successful outcome was defined as improvement or resolution of extraesophageal symptoms.

Results There were 20 patients identified. Antireflux surgery led to a successful outcome in 14 patients (70 %). Restech better identified patients with extraesophageal symptoms who had a successful outcome with antireflux surgery (12 of 14 [86 %] based on abnormal Restech versus 5 of 10 [50 %] based on abnormal proximal probe, $p = 0.06$). Comparing only the 15 patients who had both

proximal esophageal and pharyngeal pH monitoring, Restech again better identified those who had a successful outcome with antireflux surgery (9 of 10 [90 %] based on abnormal Restech versus 5 of 10 [50 %] based on abnormal proximal probe, $p = 0.05$). The positive and negative predictive values for symptomatic improvement after a fundoplication were better for an abnormal Restech score than for an abnormal proximal esophageal score (80 vs. 71 % and 60 vs. 38 %, respectively). In two patients with a successful outcome, Restech was the only positive test.

Conclusions In patients with extraesophageal reflux symptoms, proximal esophageal pH monitoring failed to identify half of the patients who had a successful outcome after antireflux surgery. In contrast, an abnormal Restech pH test was present in 90 % of patients with a successful outcome. Further, a negative Restech study more reliably indicated the absence of reflux-induced extraesophageal symptoms. Our results indicate that Restech pharyngeal pH monitoring should be utilized in the evaluation of patients with extraesophageal symptoms that may be associated with reflux disease.

Keywords Extraesophageal reflux · Fundoplication · Antireflux surgery · Pharyngeal pH monitoring · Dual probe pH monitoring · GORD/GERD (gastroesophageal reflux disease)

Presented at the SAGES 2013 Annual Meeting, April 17–20, 2013, Baltimore, MD, USA.

S. G. Worrell · S. R. DeMeester (✉) · C. L. Greene ·
D. S. Oh · J. A. Hagen
Division of Thoracic Foregut Surgery, Department of Surgery,
Keck School of Medicine, University of Southern California,
1510 San Pablo St., Suite 514, Los Angeles, CA 90033, USA
e-mail: steven.demeester@med.usc.edu

S. G. Worrell
e-mail: stephanie.worrell@med.usc.edu

Gastroesophageal reflux disease (GERD) affects more than 100 million Americans [1–3]. The most common symptoms are heartburn and regurgitation, but some patients are troubled by cough, hoarseness, frequent throat clearing, throat discomfort, or asthma symptoms alone or in addition to heartburn and regurgitation. These so-called extraesophageal symptoms can be caused or exacerbated by

GERD, but other potential etiologies include postnasal drip, allergies, sinusitis, and chronic bronchitis [4].

The clinical challenge in these patients is to determine whether GERD is a causative or contributing factor for the extraesophageal symptoms. A common approach is an empiric trial of proton pump inhibitor therapy, and if there is significant improvement, it is likely that GERD is associated with the extraesophageal symptoms [5]. Often, though, the symptomatic improvement on proton pump inhibitors is minor and the role of GERD in the extraesophageal symptoms remains unclear. In these patients, ambulatory esophageal pH testing has been used to select patients who might benefit from antireflux surgery. Patients with documented increased esophageal acid exposure in the distal esophagus often experience resolution or improvement in their extraesophageal symptoms with a Nissen fundoplication [6, 7].

Almost 20 years ago, it was shown that 12 % of patients with normal distal esophageal acid exposure will have abnormal proximal reflux when dual-probe pH monitoring is performed [8]. Subsequent studies have attempted to use dual-probe pH monitoring to better identify patients with extraesophageal symptoms who might benefit from antireflux surgery [9–12]. Ideally the proximal probe should be positioned as high in the esophagus as possible, but a limitation of these probe designs has been that if they were located above the upper esophageal sphincter, they dry out and the pH measurements become unreliable. Recently a novel pH device has been developed, the Restech pH measurement system (Respiratory Technology Corp., San Diego, CA, USA). The design of this pH probe is such that it can be positioned above the upper esophageal sphincter in the pharynx, and its unique teardrop shape prevents drying of the catheter. It is able to detect both liquid and acidic gas vapor, and the more consistent pharyngeal placement may lead to more reliable results [13]. Normal values for pharyngeal acid exposure using this device have recently been published [13].

The aim of this study was to determine whether proximal esophageal monitoring with a dual-probe pH catheter or pharyngeal pH monitoring using the Restech system better identified patients with extraesophageal symptoms that improved after antireflux surgery.

Materials and methods

Patients

A retrospective chart review was performed of all patients who had pharyngeal pH monitoring with the Restech system (Respiratory Technology Corp., San Diego, CA, USA) and underwent antireflux surgery from May 2008 to

February 2013. Preoperative testing also included conventional ambulatory pH monitoring with either a Bravo capsule (Medtronic, Shoreview, MN, USA) or a dual-probe pH catheter (Given Imaging, Duluth, GA, USA), esophageal manometry, endoscopy, and a barium videoesophagram.

Follow-up consisted of symptomatic evaluation and a barium videoesophagram at 3 months, 12 months, and annually. A successful outcome was defined as resolution or improvement in extraesophageal symptoms. This study was approved by the institutional review board of the University of Southern California.

pH testing

All patients had esophageal pH monitoring with either a wireless Bravo capsule or a dual-probe catheter, and on a different day the Restech pharyngeal system. Patients were instructed to discontinue any proton pump inhibitor medications 2 weeks before pH testing. Both the Bravo and the dual-probe catheter were positioned precisely 5 cm above the upper border of the manometrically identified lower esophageal sphincter (LES). For dual-probe pH monitoring, we selected from three different catheters that had a distance between pH sensors of 10, 15, or 18 cm such that the proximal sensor would be located as close as possible to the lower border of the upper esophageal sphincter while staying below it [14].

Pharyngeal pH testing was performed using the Restech pH probe, which has an antimony sensor at the tip and an LED light to aid in catheter placement. The catheter is inserted transnasally and advanced until the flashing LED is seen in the back of the subject's throat, 5–10 mm below the uvula. The probe measures the change in voltage potential relative to the pH of the surrounding environment twice every second. The probe is less than 1 mm in diameter, and the sensor is mounted to the tip. The size and position of the probe allow condensation from each exhaled breath to keep the sensor moist. The results are transmitted to a recorder worn by the patient [13].

An abnormal Bravo pH test was defined as a Bravo DeMeester score of >14 on either day of the study [15]. Patients who had a dual-probe pH test could have abnormal results in the distal probe only, proximal probe only, or both probes. An abnormal result at the distal probe was defined as a DeMeester score greater than 14.76. An abnormal result at the proximal probe was defined as a composite score greater than 16.4 [14].

An abnormal Restech score was based on the Ryan score developed by Ayazi et al. [13]. The score was calculated from 55 normal subjects, using the 95th percentile for time with pH less than 4, 4.5, 5, 5.5, 6, and 6.5. A mathematical model was used to find the best discriminating pH

threshold. The best pH threshold was found to differ on the basis of position and was 5.5 when upright and 5.0 when supine. These thresholds were then used to calculate a score for normal pharyngeal exposure, called the Ryan score, using the same methodology as was used to develop the composite pH score for esophageal pH monitoring. An abnormal Ryan score in the upright position is greater than 9.4 while in the supine position a Ryan score above 6.8 is abnormal. Patients abnormal in either the upright or supine periods by the Ryan score were considered to have a positive Restech study [13].

Motility study

Patients underwent either high-resolution manometry or a conventional motility study using a water-perfused catheter. High-resolution manometry was performed with the patient in the supine position using the Sierra system (Given Imaging, Duluth, GA, USA) as previously described [16]. A defective LES was defined as a total length less than 2.7 cm, an abdominal length less than 1 cm, or a resting pressure less than 13 mm Hg. The esophageal body was defined as abnormal if there were more than 50 % ineffective swallows or the mean wave amplitude was greater than 152 mm Hg or less than 43 mm Hg [17]. Conventional motility was performed as previously described [18]. Using a stationary pull-through technique, the LES was considered abnormal when the total length was less than 2 cm, the abdominal length was less than 1 cm, or the resting pressure less than 6 mm Hg. The esophageal body was defined as abnormal if there were more than 30 % ineffective swallows or the mean wave amplitude was greater than 180 mm Hg or less than 30 mm Hg [18].

Data analysis and statistical methods

All values are reported as median unless otherwise noted. Comparisons were performed by contingency tables and the Mann–Whitney *U* test for ordinal values. Values less than 0.05 were considered statistically significant. Statistical analysis was performed by Prism 4 statistical software (GraphPad, San Diego, CA, USA).

Results

There were 20 patients with GERD and extraesophageal reflux symptoms who had Restech pharyngeal pH monitoring and underwent antireflux surgery. Patient characteristics are shown in Table 1. The presenting extraesophageal symptoms were hoarseness (65 %), cough (65 %), asthma (40 %), and globus (30 %). In 80 % of

Table 1 Patient characteristics and endoscopic findings

Characteristic	Value
No. of patients	20
Sex, M:F	8:12
Age, y	59 (22–80)
Presenting symptoms	
Atypical alone	4 (20 %)
Atypical + typical	16 (80 %)
Hiatal hernia size, cm	2
Barrett esophagus	5 (25 %)
Esophagitis	3 (15 %)

patients, typical reflux symptoms were also present. In contrast to typical reflux disease, extraesophageal symptoms with or without typical GERD symptoms were more common in women. Motility studies showed the LES and esophageal body were manometrically normal in 75 % of patients.

Ambulatory pH monitoring included distal esophageal and pharyngeal pH monitoring in all 20 patients, and in 15 patients proximal esophageal acid exposure was evaluated with a dual-probe catheter. There was increased esophageal acid exposure in the distal esophagus in 75 % of patients, in the proximal esophagus in 47 % (7 of 15), and in the pharynx in 75 % (15 of 20) of patients. A positive pH test was present at one or more locations in all but two patients. The two patients with normal ambulatory pH monitoring scores underwent antireflux surgery either due to a borderline score with abnormal number of reflux episodes both distally and proximally or the presence of Barrett esophagus. Only 5 of the 15 patients (33 %) with both proximal esophageal pH monitoring using a dual-probe catheter and pharyngeal pH monitoring with the Restech were abnormal with both techniques.

The antireflux procedure was a Nissen fundoplication in 17 and a Toupet in three patients. Follow-up videoesophagrams were available from 12 patients at 3 months and three patients at 12 months after surgery. There were no recurrent hiatal hernias, but the fundoplication appeared to have disrupted in one patient. Symptomatic follow-up was available from all 20 patients at a median of 18 months. There were 14 patients (70 %) who experienced improvement in their extraesophageal symptoms. Compared to typical symptoms and hoarseness, cough and asthma were less likely to improve. Table 2 shows the relationship between symptomatic outcome and the results of proximal esophageal versus pharyngeal pH monitoring. Restech better identified patients with extraesophageal symptoms who had a successful outcome with antireflux surgery (12 of 14 [86 %] based on abnormal Restech versus 5 of 10 [50 %] based on abnormal proximal probe, $p = 0.06$).

Table 2 Symptomatic outcomes with proximal esophageal and pharyngeal pH monitoring

Symptom improvement	Normal proximal probe (<i>n</i> = 8)	Abnormal proximal probe (<i>n</i> = 7)	Normal Restech score (<i>n</i> = 5)	Abnormal Restech score (<i>n</i> = 15)
Yes	5 (63 %)	5 (71 %)	2 (40 %)	12 (80 %)
No	3 (37 %)	2 (29 %)	3 (60 %)	3 (20 %)

Table 3 Proximal esophageal and pharyngeal (Restech) scores in five patients with normal esophageal acid exposure in the distal esophagus

Patient no.	Distal pH score, day 1/day 2	Proximal esophageal pH score	Restech score, upright/supine	Symptomatic improvement
1	14.4/NA	Normal (12.4)	Normal (3.89/2.17)	No
2	3/NA	Normal (3)	Abnormal (36.4/2.17)	No
3	3.5/5.1	NA	Abnormal (63.3/37.18)	Yes
4	13.7/NA	Normal (11.9)	Normal (2.12/2.95)	No
5	1.7/1.4	NA	Abnormal (2.4/26.6)	Yes

NA not assessed

Comparing only the 15 patients who had both proximal esophageal and pharyngeal pH monitoring, Restech again better identified those who had a successful outcome with antireflux surgery (9 of 10 [90 %] based on abnormal Restech versus 5 of 10 [50 %] based on abnormal proximal probe, $p = 0.05$). The positive and negative predictive values for symptomatic improvement after a fundoplication were better for an abnormal Restech score than for an abnormal proximal esophageal score (80 vs. 71 % and 60 vs. 38 %, respectively).

Normal distal esophageal acid exposure was present in five patients. In three of these patients, the Restech pharyngeal probe was the only abnormal study, and two of the three patients experienced improvement after the fundoplication (Table 3). The two patients with normal scores at every site were not improved with the fundoplication.

Discussion

Extraesophageal symptoms that may be related to gastroesophageal reflux include cough, hoarseness, throat discomfort, frequent throat clearing, and asthma. There are two mechanisms proposed for how gastroesophageal reflux can produce these types of symptoms. One is a *reflex* mechanism and the other a *reflux* mechanism. The reflex mechanism involves reflux stimulation of vagal afferents which subsequently produces laryngeal and pulmonary effects via vagal efferents from the dorsal motor nucleus. In this mechanism, proximal reflux of gastric juice is not necessary. The other concept is the reflux mechanism in which there is direct irritation of sensitive laryngeal and pharyngeal tissues by gastric juice that is refluxed all the way up to the pharynx and larynx [19].

Acid suppression medications are generally the first line of therapy for patients with suspected reflux-induced respiratory or extraesophageal symptoms. Commonly

patients are first referred to an otolaryngologist, and when a red appearance to the larynx or vocal cords is noted on a direct laryngoscopy, the patients are told that reflux is likely the source of their symptoms, and acid suppression therapy is initiated. Eventually many of these patients are referred for consideration of a fundoplication because the symptom relief with medical therapy is often limited or minimal, likely related to the fact that acid suppression medications alter the pH of the refluxed material but do not change the number of reflux events [20]. Continued reflux of weakly acidic gastric contents can perpetuate extraesophageal symptoms because even sporadic reflux episodes have been shown to be sufficient to induce chronic inflammation in the sensitive mucosa of the pharynx, larynx, and trachea [19, 21].

Antireflux surgery has an established role for relief of typical symptoms including heartburn and regurgitation, and a number of studies have also shown the efficacy of antireflux surgery for relief of extraesophageal symptoms [22, 23]. The challenge is to identify the patients most likely to have reflux as the major or sole etiology for their extraesophageal symptoms, given the frequently multifactorial nature of these symptoms. The multifactorial etiology of extraesophageal symptoms is likely the reason that there were two patients with abnormal distal and proximal esophageal acid exposure who did not improve and a further two patients with an abnormal distal score and an abnormal Restech pharyngeal score who also did not improve. In this series, we performed a fundoplication on two patients with normal distal and proximal esophageal and/or Restech pharyngeal pH monitoring, and neither patient experienced improvement in their extraesophageal symptoms. This emphasizes the importance of documenting increased esophageal acid exposure in these patients. The majority of patients had an abnormal score in the distal esophagus (75 %), and with that finding alone, 80 % of the time, extraesophageal symptoms improved after

fundoplication. However, the use of Restech identified two patients with normal distal esophageal acid exposure who had abnormal pharyngeal reflux based on the Ryan score and were symptomatically improved with a fundoplication. All told, of the 14 patients who improved after fundoplication, an abnormal Restech was present in 12 (86 %) of these patients and was the test with the highest positive predictive value (80 %). Further, of the five patients with a normal Restech Ryan score, three had no improvement with a fundoplication, and Restech had the highest negative predictive value (60 %). Consequently, Restech pharyngeal pH monitoring can be used to reliably tell patients with extraesophageal symptoms that their symptoms are unlikely to be related to reflux disease.

Despite reports suggesting that 12 % of patients with normal distal esophageal acid exposure have increased acid exposure in the proximal esophagus when a dual-probe study is performed, this pattern was not seen in any of our 20 patients [8]. Instead, the only patients with an abnormal score proximally in the esophagus were those with an abnormal distal score. Further, the combination of an abnormal score distally and proximally in the esophagus was not more useful for identifying patients whose extraesophageal symptoms improved after antireflux surgery than a positive distal score alone. Of the 15 patients who had dual-probe monitoring, 10 had symptomatic improvement with a fundoplication, and only five of these had a positive proximal probe. The likelihood of improvement of extraesophageal symptoms after antireflux surgery was similar whether the proximal probe was positive (71 %) or negative (63 %). Further, the low negative predictive value for a normal score at the proximal probe (37 %) precludes this test from reliably selecting out patients with extraesophageal symptoms who are unlikely to benefit from an antireflux operation.

An important distinction between proximal esophageal monitoring and Restech pharyngeal monitoring is the pH value used for determination of reflux. Proximal esophageal monitoring uses a pH of 4, the same pH as is used in the distal esophagus, but with different thresholds for each parameter. The thresholds for abnormal proximal acid exposure are 24 reflux events, a percentage time pH < 4 of 0.8, and a composite score of 16.4 [14]. In comparison, after studying a series of normal subjects with the Restech system, two different pH values were selected. The best discriminating pH values were 5.5 and 5 for the upright and supine positions, respectively [13]. This is one important potential explanation for why pharyngeal pH monitoring outperformed proximal esophageal pH monitoring in this series. It is likely that a pH of 4 is not the best discriminator for reflux-induced extraesophageal symptoms. In a prior study of patients with laryngopharyngeal reflux symptoms we noted that loss of alkalinity (percentage time pH \geq 7) in the proximal pH probe was a better indicator for relief of

symptoms after an antireflux operation than was acid exposure using percentage time pH < 4 [24].

This study thus suggests that the most reliable method to identify patients with extraesophageal symptoms likely to benefit from an antireflux operation is with a combination of distal esophageal pH monitoring with the Bravo probe and pharyngeal pH monitoring with the Restech system. Use of only a Bravo probe would have missed two patients with normal distal esophageal acid exposure but abnormal pharyngeal exposure whose symptoms improved with an antireflux operation. Similarly, evaluating these patients with only pharyngeal pH monitoring would have missed two patients with an abnormal score distally but normal pharyngeal pH that also improved. Clearly no test is perfect, and even in the setting of abnormal reflux some patients with extraesophageal symptoms achieve little or no benefit from an antireflux procedure, other than that they can now vigorously explore alternative etiologies for their symptoms. Interestingly, all nine patients with Restech scores that were 5 times the normal Ryan score had symptomatic improvement. Overall, we found that patients with both typical and atypical symptoms were more likely to improve.

There are several limitations to this study. One is the small number of patients. Another is the fact that the Restech pH monitoring was done on a different day than the Bravo or the dual-probe pH studies. We also did not look at oxygen desaturation events in this patient population. Recently there are reports that continuous pulse oximetry monitoring can help identify patients with reflux-induced extraesophageal symptoms [25]. Further studies in these difficult patients will be necessary to best define the types of testing that will most accurately select patients likely to benefit from an antireflux operation.

In conclusion, we found that in patients with extraesophageal reflux symptoms proximal esophageal pH monitoring failed to identify half of the patients who had a successful outcome after antireflux surgery. In contrast, an abnormal Restech pharyngeal pH test was present in 86 % of patients with a successful outcome. Further, a negative Restech study more reliably indicated the absence of reflux induced extraesophageal symptoms. Our results indicate that Restech pharyngeal pH monitoring should be utilized in the evaluation of patients with extraesophageal symptoms that may be associated with reflux disease.

Disclosures Drs. Stephanie G. Worrell, Steven R. DeMeester, Christina L. Greene, Daniel S. Oh, and Jeffrey A. Hagen have no conflicts of interest or financial ties to disclose.

References

1. Spechler SJ (1992) Epidemiology and natural history of gastro-oesophageal reflux disease. *Digestion* 51:24–29

2. Moayyedi P, Talley NJ (2006) Gastro-oesophageal reflux disease. *Lancet* 367:2086–2100
3. Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R (2006) The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 101:1900–1920
4. Hom C, Vaezi MF (2013) Extraesophageal manifestations of gastroesophageal reflux disease. *Gastroenterol Clin North Am* 42:71–91
5. Nord JH (2004) Extraesophageal symptoms: what role for the proton pump inhibitors? *Am J Med* 117:568–628
6. Lindstrom DR, Wallace J, Loehrl TA, Merati AL, Toohill RJ (2002) Nissen fundoplication surgery for extraesophageal manifestations of gastroesophageal reflux (EER). *Laryngoscope* 112:1762–1765
7. Sala E, Salminen P, Simberg S, Koskenvuo J, Ovaska J (2008) Laryngopharyngeal reflux disease treated with laparoscopic fundoplication. *Dig Dis Sci* 53:2397–2404
8. Schantz PF, Castell JA, Castell DO (1996) Pulmonary symptoms associated with gastroesophageal reflux: use of ambulatory pH monitoring to diagnose and to direct therapy. *Am J Gastroenterol* 91:1715–1718
9. Kirkby-Bott J, Jones E, Perring S, Hosking SW (2011) Proximal acid reflux treated by fundoplication predicts a good outcomes for chronic cough attributable to gastro-oesophageal reflux disease. *Langenbecks Arch Surg* 396:167–171
10. Theodoropoulos DS, Ledford DK, Lockey RF, Pecoraro DL, Rodriguez JA, Johnson MC, Boyce HW (2001) Prevalence of upper respiratory symptoms in patients with symptomatic gastroesophageal reflux disease. *Am J Respir Crit Care Med* 164:72–76
11. Issing WJ, Karkos PD, Perreas K, Folwaczny C, Reichel O (2004) Dual-probe 24-h ambulatory pH monitoring for diagnosis of laryngopharyngeal reflux. *J Laryngol Otol* 118:845–848
12. Novitsky YW, Zawacki JK, Irwin RS, French CT, Hussey VM, Callery MP (2002) Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. *Surg Endosc* 16:567–571
13. Ayazi S, Lipham JC, Hagen JA, Tang AL, Zehetner J, Leers JM, Oezcelik A, Abate E, Banki F, DeMeester SR, DeMeester TR (2009) A new technique for measurement of pharyngeal pH: normal values and discriminating pH threshold. *J Gastrointest Surg* 13:1422–1429
14. Ayazi S, Hagen JA, Zehetner J, Oezcelik A, Abate E, Kohn GP, Sohn HJ, Lipham JC, DeMeester SR, DeMeester TR (2010) Proximal esophageal pH monitoring: improved definition of normal values and determination of a composite pH score. *J Am Coll Surg* 210:345–350
15. Ayazi S, Lipham JC, Portale G, Peyre CG, Streets CG, Leers JM, DeMeester SR, Banki F, Chan LS, Hagen JA, DeMeester TR (2009) Bravo catheter-free pH monitoring: normal values, concordance, optimal diagnostic thresholds, and accuracy. *Clin Gastroenterol Hepatol* 7:60–67
16. Carlson DA, Pandolfino JE (2013) High-resolution manometry and esophageal pressure topography: filling the gaps of convention manometry. *Gastroenterol Clin North Am* 42:1–15
17. Bredenoord AJ, Fox M, Kahrilas PJ, Pandolfino JE, Schwizer AJ, Smout AJ (2012) Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal topography. *Neurogastroenterol Motil* 24:57–65
18. Spechler SJ, Castell DO (2001) Classification of oesophageal motility abnormalities. *Gut* 49:145–151
19. Morice AH (2008) Is reflux cough due to gastroesophageal reflux disease or laryngopharyngeal reflux? *Lung* 186:103–106
20. Hershcovici T, Fass R (2011) Gastro-oesophageal reflux disease: beyond proton pump inhibitor therapy. *Drugs* 71:2381–2389
21. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO (2006) Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut* 55:1398–1402
22. Swager J, Ponsky J, Hicks DM, Richter JE, Abelson TI, Milstein C, Qadeer MA, Vaezi (2006) Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression. *Clin Gastroenterol Hepatol* 4:433–441
23. Mainie I, Tutuian R, Agrawal A, Adams D, Castell DO (2006) Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-esophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 93:1483–1487
24. Ayazi S, Hagen JA, Zehetner J, Lilley M, Wali P, Augustin F, Oezcelik A, Sohn HJ, Lipham JC, DeMeester SR, DeMeester TR (2010) Loss of alkalization in proximal esophagus: a new diagnostic paradigm for patients with laryngopharyngeal reflux. *J Gastrointest Surg* 14:1653–1659
25. Wilshire CL, Salvador R, Sepesi B, Niebisch S, Watson TJ, Little VR, Peyre CG, Jones CE, Peters JH (2013) Reflux-associated oxygen desaturations: usefulness in diagnosing reflux-related respiratory symptoms. *J Gastrointest Surg* 17:30–38