Chapter 12
Diagnostic Approach to Laryngopharyngeal Reflux

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Introduction

The diagnosis of laryngopharyngeal reflux (LPR) presents significant challenges despite its first being recognized as a distinct clinical entity decades ago. There remains considerable controversy over what the most reliable diagnostic criteria are and what diagnostic modality is preferred. There is no gold standard [1]. Currently, a combination of clinical history, physical findings on laryngoscopy, and a variety of somewhat nonspecific tests are employed by practitioners to evaluate patients with suspected LPR. In this chapter, we will detail a variety of available diagnostic options for LPR, presenting the advantages and the disadvantages of each.

Barium Esophagram

The barium esophagram, or barium swallow, is one of the oldest diagnostic tests for evaluation of upper gastrointestinal disorders predating modern endoscopy. It remains a useful screen for luminal disorders including stricture, tumors, and hiatal hernia. It may demonstrate backflow but has a significant false-negative rate, thus limiting its benefit in patients with suspected LPR. Kimura et al. demonstrated barium esophagram as a useful predictor of response to empiric treatment [2], but it offers no practical advantages over therapeutic trial.

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Therapeutic Trial

Empiric therapeutic trial of antisecretory therapy with acid-reducing agents, in particular, twice daily proton pump inhibitors, has long been felt by many to be the most optimum approach in patients with suspected LPR. In fact, in 2009 the American Academy of Otolaryngology published guidelines on hoarseness wherein patients were evaluated with a reflux symptom index and reflux finding score [3]. If greater than 13 or 7, respectively, Ford recommended empiric treatment with twice daily PPI therapy for 3–6 months and pH monitoring for patients who failed to show improvement after the initial 3 months [4]. Despite the accepted safety of PPI therapy, it is suggested that there are significant rates of adverse events including, but not limited to, osteoporosis, an increased rate of pneumonia [5], increased potential for rates of cardiovascular disease [6], nephrotoxicity [7], hepatotoxicity [8], and greater risk for cancer of the esophagus and stomach [9]. In addition, much has been written about the association of PPI use and cognitive impairment; however, Goldstein et al. [10] and other authors had confirmed this concern that continuous PPI use does not cause cognitive decline [11, 12]. These studies suggest a potential correlation in large-scale data analysis that long-term PPI use might confer an increase in risk to these various diseases and certainly to at-risk populations. However, interpretation of retrospective data and large cohort studies must be weighed against potential benefits. The primary goal should be to limit the use of long-term pharmacotherapy. Most authors recommend 8–12 weeks of empiric twice daily PPI therapy in combination with lifestyle modifications for patients with suspected LPR [13].

Therapeutic trial is a reasonable initial approach in patients with suspected laryngopharyngeal reflux disease; however, the subjective nature of symptom reporting, as well as the inter- and intra-observer variability, calls this approach into question. In addition, controlled studies have demonstrated symptom improvement in placebo groups. Given the aforementioned concerns in regard to long-term PPI use, diet and lifestyle modifications should be an additional consideration. Zalvan et al. demonstrated that alkaline water, a Mediterranean-style, plant-based diet, and standard reflux precautions were equally as effective in reducing the reflux symptom index (RSI) than reflux precautions and PPI therapy [14]. For patients who are unable to comply with dietary and lifestyle modifications, we currently favor 6–8 weeks of therapeutic trial with diagnostic testing reserved for nonresponders [10, 12].

pH Monitoring

There are a variety of ambulatory pH monitoring technologies available to evaluate patients with reflux-related upper aerodigestive tract disorders. These include single- or double-probe catheter-based systems, multichannel intraluminal impedance

(MIIpH), wireless telemetry pH capsules, and oropharyngeal monitoring. Katz suggested that monitoring was indicated in patients who failed empiric therapy or in whom the diagnosis of GERD or LPR was suspected [15].

Single- or double-probe catheter-based pH monitoring is useful to accurately define acid exposure in both distal and proximal esophagus. Their utility remains problematic because of the potential role of non- or weakly acidic reflux producing symptoms similar to LPR. In addition, catheter-based pH testing requires nasal intubation and is poorly received by patients. However, positive pH studies coupled with suggestive RSI and RSF scores are predictive of success of anti-reflux therapy. Intraluminal impedance testing in the esophagus measures directional bolus movement. In combination with pH testing, impedance can help categorize reflux events into acid, weakly acid, or nonacid [16]. However, even though multi-luminal impedance testing (MIIpH) may identify more refluxers and better categorize them, Sanagapalli et al. demonstrated no clear evidence that extrapolates into better treatment for these patients [17]. Again, there is no gold standard diagnostic test to compare. MIIpH is fraught with technical issues such as catheter placement, pH sensor placement, and interpretation. Esophageal parameters are typically reported using the DeMeester score which does not correlate well with oropharyngeal pH events and symptoms. Additionally, acidic changes within the oropharynx are influenced by oral intake of foods and liquids as well as nasal drainage which can influence the oropharyngeal pH measurement.

The wireless pH capsule provides a safe, effective non-catheter-based system that is inserted endoscopically. The capsule remains in place for up to 96 hours and in general is well tolerated. The capsule detaches and passes through the GI tract. There are significant limitations for the diagnosis of LPR including the inability to detail proximal acid exposure, the necessity for endoscopy, the ability to detail only strongly acidic events of pH less than 4, and the inability to provide impedance data limit this technology's utility. The pH capsule may be a useful tool in assessing patients with both typical and atypical GERD symptoms. It has limited value in patients with suspected LPR without classic GERD symptom etiology.

One of the most recent developments in pH testing is the oropharyngeal pH probe (Restech DX-pH probe, Respiratory Technology Corporation, Houston, TX, USA). The procedure involves the trans-nasal placement of a small-diameter catheter in the posterior oropharynx. This tube monitors liquids and aerosolized acid and connects wirelessly to a monitor worn by or in close proximity to the patient. Several studies have demonstrated the reliability of this technique in demonstrating oropharyngeal reflux events [18, 19]. The Ryan score, created by Dr. Tom Ryan DeMeester, is proprietary to the Restech software and defines normal values while identifying patients with abnormal pharyngeal pH environments. It is a composite that is generated by measuring the percent time pH below 5.5 while upright and below 5.0 while supine, the number of episodes where pH droops below the thresholds, and the duration of the longest reflux episode. A positive Ryan score is diagnostic of significant oropharyngeal reflux [20].

However, Weiner et al. showed a poor correlation of oropharyngeal testing when compared to multichannel intraluminal impedance and pH monitoring [18, 19]. Friedman concluded that there were no pretest indicators of positive or negative testing suggesting the frequent need for objective evaluation [21]. Also, it has been demonstrated that oropharyngeal acid exposure does not predict symptom response to PPI therapy [22]. Again, the lack of a gold standard and typical comparison to DeMeester score and esophageal findings as well as small sample size limit the power of these studies. Given the overlap of laryngopharyngeal symptoms of LPR with other upper aerodigestive diseases including states of hypersensitivity, reflux symptom scores are often overinflated leading to misdiagnosis of LPR as the cause of the symptom complex. Oropharyngeal pH testing is instrumental in measuring acidic conditions within the oropharynx. In situations of elevated symptom scores but a negative oropharyngeal pH measurement, neurosensory changes with localized hypersensitivity should be entertained, as is often the case with chronic neurogenic cough. In the situation of an elevated symptom score with positive Ryan score with strong correlation of symptoms to reflux events, LPR is likely the cause, though both reflux and hypersensitivity states can coexist. Thus, oropharyngeal pH testing is an excellent tool to guide treatment options, especially in the patient who has seen multiple doctors from multiple specialties for their oro-laryngopharyngeal symptoms.

There is debate about whether patients who are to undergo pH testing should be tested on or off acid suppression medication. Pritchett et al. [23] evaluated 39 patients with refactory symptoms who had pH impedance monitoring on acid suppression therapy and subsequently monitored the same group of patients with pH testing off therapy. Of the patients on therapy, 25 (64%) had normal results. 28 (72%) had abnormal results off therapy. The authors concluded that pH impedance testing on therapy is preferred since it better predicts baseline acid reflux and thus provides more useful clinical information [24].

A wide range of opinions exists about the efficacy of various diagnostic tests for LPR. Many patients with LPR symptoms have neurosensory changes and hypersensitivity as a cause of their symptoms. pH testing is useful in demonstrating an absence of reflux in patients with vaguely mediated hypersensitivity as well as confirming the presence of reflux, supporting and reinforcing with patients the need for treatment. pH impedance testing is able to detect acid, nonacid, and gaseous fluid, but it is uncomfortable for patients, can be difficult to interpret, and does not predict severity of disease.

Oropharyngeal pH monitoring is better tolerated, equally sensitive, and easier to perform and interpret. pH telemetry capsule testing requires endoscopy and provides accurate data but only measures pH at the distal esophagus.

As mentioned, there is differing opinions as to which modality is preferred. Many authors have highlighted the problems with sensitivity and specificity of all diagnostic tests for LPR. We favor oropharyngeal testing as an initial approach to patients that require pH monitoring [25]. If a trial of dietary and lifestyle changes does not effect significant improvement in symptoms and symptom scores, then oropharyngeal pH testing can be useful in determining the presence of absence of acid. The technology itself is highly sensitive to changes in pH. If a test is performed and the patient is symptomatic during testing yet there is no acid present, the potential for neurosensory changes is heightened, and treatment and counseling can be appropriately directed. Conversely, a patient who is noncompliant on dietary and lifestyle changes can be presented with oropharyngeal pH data demonstrating significant episodes of acid exposure, and correlation with symptoms can either be counseled on the importance of significant dietary and lifestyle changes or be offered pharmacological interventions, with appropriate discussions of potential risks. Typically pharmacological intervention should be used as a bridge to allow time for diet and behavioral change and weight loss with an overall goal to dietary changes trending more toward a plant-based, Mediterranean-style diet. Pharmaceuticals, like alkaline water, or coating agents, such as alginates, should be viewed as more a “band-aid” than a definitive treatment, whereas dietary change should be encouraged as the cure.

Salivary Pepsin

Salivary pepsin testing is an inexpensive, noninvasive test that may represent a reasonable diagnostic alternative. Although laryngeal mucosa can be resistant to acid exposure of a pH greater than 4 [26], studies have shown that pepsin can cause laryngeal mucosal damage in mildly acidic and even alkaline environments [26, 27]. Ocak et al. showed a high specificity rate of a positive salivary pepsin test in predicting LPR; however, they demonstrated a low sensitivity rate perhaps due to sample collection frequency [26]. These findings were confirmed in subsequent studies suggesting positive salivary pepsin tests could be considered diagnostic for LPR, but a negative study does not rule this out. The latter group of patients need to undergo additional diagnostic testing [27]. Timing of testing, typically morning, and multiple testing samples throughout the day will likely provide greater sensitivity and specificity for an LPR diagnosis. Salivary testing remains a potentially promising test when combined with pH testing to further identify those patients at risk for laryngopharyngeal tissue damage and inflammation. What remain to be determined and studied are the multiple neurosensory changes that can occur resulting in altered levels of sensitivity. Changes in neuronal sensitivity mediated by upregulation of acid receptors could potentially cause symptoms even in the presence of weak levels of acid, possibly potentiated by the presence of pepsin. High levels of pepsin in the presence of an acidic environment with no significant neuronal change likely will be highly predictive of LPR. Future studies looking at the oropharyngeal pH, levels of extra- and intracellular pepsin, better characterization of neuronal sensitivity with levels of transient receptor potential, TRP channels and acid-sensing ion channel (ASIC) receptors as well as more complete characterizations of symptoms, such as the reflux symptom score (RSS), will become the gold standard in diagnosing LPR [28].

High-Resolution Manometry

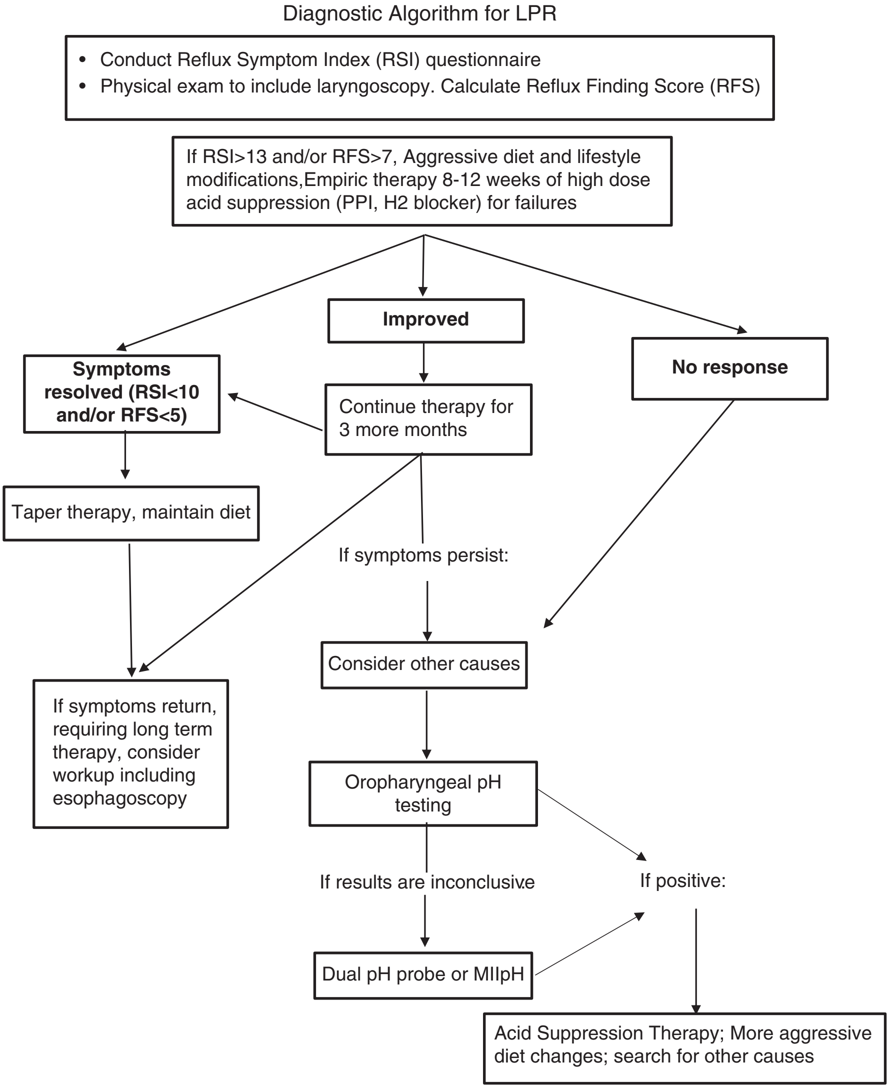
In patients with known LPR whose symptoms persist despite high-dose PPI therapy, other diagnoses including but not limited to allergies, sinus disease, and asthma are considered to be causative [29]. However, reflux disease cannot adequately be ruled out by PPI treatment failure. Nonacid reflux and breakthrough acid reflux may exist [30]. Impedance testing in addition to high-resolution monitoring may be useful in evaluating these patients. Impedance testing can detect any reflux and determine the frequency and direction, while manometry can determine if the upper esophageal sphincter and lower esophageal tone are normal during activation and relaxation, as well as assess peristalsis [31]. However, it is unclear how impedance and manometry may affect management of patients with LPR who have failed high doses of PPIs. Carol et al. demonstrated nonacid reflux and breakthrough acid reflux in 74% of 54 patients with presumed LPR who failed empiric high-dose PPI therapy [29]. These diagnoses would have been missed by traditional pH testing. Furthermore, eight patients had esophageal motility as a cause of their symptoms. In patients who fail adequate dietary and behavioral change, despite aggressive education, and then fail subsequent pharmaceutical intervention, the index of suspicion for esophageal dysmotility should be raised. Many of the symptoms within the RSI can be mimicked by other diseases and neurosensory change. Post-viral vagal neuropathies can cause motor and sensory changes resulting in laryngopharyngeal hypersensitivity. As the vagus is the major motor nerve of the esophagus and stomach, these neurosensory changes can be accompanied by esophageal and gastric motor dysfunction resulting in a variety of symptoms that are poorly controlled with dietary changes or pharmaceuticals and a combination. The combination of impedance and high-resolution manometry proved valuable in the direction of therapy for all patients. Poorly controlled symptoms in patients with significant dysmotility also suggest a potential decreased outcome with surgical intervention. Further studies, perhaps with the inclusion of pharyngeal impedance, will be necessary to determine the role of impedance and manometry testing in the diagnosis of patients with LPR.

Reflux Scintigraphy

There is no clear-cut definition of gastroesophageal reflux disease (GERD). As mentioned previously, there is also no gold standard diagnostic criteria for laryngopharyngeal reflux (LPRD). We have previously discussed the advantages and limitations of a variety of pH monitoring techniques. Reflux scintigraphy is a safe, cost-effective, noninvasive technique that offers a valuable screening tool in patients with suspected LPR. To perform reflux scintigraphy, patients are positioned upright and asked to swallow a technetium-based tracer mixed with water while dynamic images are taken with a gamma camera. Falk et al. demonstrated a greater percentage of proximal reflux and aspiration in LPR than in patients with classic GERD and as expected demonstrated greater rates of reflux in both groups while patients were supine [32]. Their study was limited due to its retrospective nature and different reported standards for scintigraphy. Nevertheless, scintigraphy remains an interesting option for distinguishing patients with LPR and aspiration associated with GERD [32].

Conclusion

In conclusion, we feel that the best initial approach to most patients with suspected LPR should be a 6–8-week therapeutic trail. (Diagnostic Algorithm) We find barium esophagram could be of minimal value in further evaluation. Oropharyngeal testing despite its limitations does offer a minimally invasive, well-tolerated diagnostic technique that is usually of significant help in directing reflux therapy. Dual-channel pH monitoring with or without impedance can help categorize in better detail reflux disorders but may not offer any better direction in the selection of therapies. The telemetry capsule does provide the longest data recording but has limited value in proximal and nonacid reflux disease. Salivary pepsin and scintigraphy are interesting options that may serve as a screening or objective role in the evaluation of these patients, but more retrospective studies are needed to better assess their place in the LPR diagnostic paradigm.



References

1. Wright MR, Sharda R, Vaezi MF. Unmet needs in treating laryngo-pharyngeal reflux disease: where do we go from here? Expert Rev Gastroenterol Hepatol. 2016;10(9):995.
2. Kimura Y, Sugiura M, Kato T, Makino N, Ohmae Y, Kishimoto S. Value of barium swallow studies in predicting the response to rabeprazole in elderly patients with laryngopharyngeal reflux disease and nonerosive reflux disease in particular. Ann Otol Rhinol Laryngol. 2017;119(9):631–5.

3. Stachler RJ, Francis DO, Schwartz SR, Damask CC, Digoy GP, Krouse HJ, McCoy SJ, Ouellette DR, Patel RR, Reavis CW, Smith LJ, Smith M, Strode SW, Woo P, Nnacheta LC. Clinical practice guideline: hoarseness (dysphonia) (update). Otolaryngol Head Neck Surg. 2018;158:S1–S42.
4. Ford CN. Evaluation and management of laryngopharyngeal reflux. JAMA. 2005;294(12):1534–40.
5. Falk GL, Vivian SJ. Laryngopharyngeal reflux: diagnosis, treatment and latest research. Eur Surg. 2016;48(2):74–91.
6. Shiraev P, Bullen A. Proton pump inhibitors and cardiovascular events: a systematic review. Heart Lung Circ. 2018;27(4):443–50.
7. Hart E, et al. Proton pump inhibitors and risk of acute and chronic kidney disease: a retrospective cohort study. Pharmacotherapy. 2019;39(4):443–53.
8. Llorente C, Jepsen P, Inamine T, et al. Gastric acid suppression promotes alcoholic liver disease by introducing overgrowth or intestinal enterococcus. Nat Commun. 2017;8:837.
9. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of current evidence. Ther Adv Gastroenterol. 2019;12:1–11.
10. Goldstein FC, Steenland K, Zhao L, Wharton W, Levey AI, Hajjar I. Proton pump inhibitors and risk of mild cognitive impairment and dementia. J Am Geriatr Soc. 2017;65(9):1969–74.
11. Brett AS. Evidence against an alleged association between PPIs and dementia. Review of "Taipale H et al. Am J Gastroenterol 2017 Jul 11. Lochhead P et al. Gastroenterology 2017 Jul 17." NEJM Journal Watch 2017.
12. Taipale H, Tolppanen AM, Tiihonen M. No association between proton pump inhibitor use and risk of Alzheimer's disease. Am J Gastroenterol. 2017;112(12):1802–8.
13. Sidhwa F, Moore A, Alligood E. Diagnosis and treatment of the extraesophageal manifestations of gastroesophageal reflux disease. Ann Surg. 2017;265(1):63–7.
14. Zalvan C, Hu S, Greenberg B, Geliebter J, et al. A comparison of alkaline water and mediterranean diet vs proton pump inhibition for treatment of laryngopharyngeal reflux. JAMA Otolaryngol Head Neck Surg. 2017;143(10):1029–3.
15. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–28.
16. Boeckxstaens GE, Smout A. Systematic review: role of acid, weakly acidic and weakly alkaline reflux in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2010;32: 334–43.
17. Sanagapalli S, Sweis R. Combined pH-impedance testing for reflux: current state of play and future challenges. Front Gastroenterol. 2017;8:154–5.
18. Golub JS, Johns MM III, Lim JH, DelGaudio JM, Klein AM. Comparison of an oropharyngeal pH probe and a standard duel pH probe for the diagnosis of laryngopharyngeal reflux. Ann Otol Rhinol Laryngol. 2009;118:1–5.
19. Wiener GJ, Tsukashima R, Kelly C, Wolf E, Schmeltzer M, Bankert C, et al. Oropharyngeal pH monitoring for the detection of liquid and aerosolized supraesophageal gastric reflux. J Voice. 2009;23:498–504.
20. Ayazi S, Lipham JC, Hagen JA, et al. A new technique for measurement of pharyngeal pH: normal values and discriminating pH threshold. J Gastrointest Surg. 2009;13(8):1422–9.
21. Friedman M, Hamilton C, Samuelson CG, Kelley K, Taylor R, Darling R, Taylor D, Fisher M, Maley A. The value of routine pH monitoring in the diagnosis and treatment of laryngopharyngeal reflux. Otolaryngol Head Neck Surg. 2012;146(6):952–8.
22. Yadlapati R, Pandolfino JE, Lidder AK, Shabeeb N, et al. Oropharyngeal pH testing does not predict response to proton pump inhibitor therapy in patients with laryngeal symptoms. Am J Gastroenterol. 2016;111:1517–24.
23. Pritchett JM, Aslam M, Slaughter JC, Ness RM, Garrett CG, Vaezi MF. Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. Clin Gastroenterol Hepatol. 2009;7(7):743–8.
24. Barry DW, Vaezi MF. Laryngopharyngeal reflux: more questions than answers. Cleve Clin J Med. 2010;77(5):327–34.

25. Martinucci I, de Bortoli N, Savarino E. Optimal treatment of laryngopharyngeal reflux disease. Ther Adv Chronic Dis. 2013;4(6):287–301.
26. Ocak E, Kubat G, Yurulmaz. Immunoserologic pepsin detection in the saliva as a non-invasive rapid diagnostic test for laryngopharyngeal reflux. Balkan Med J. 2015;32:46–50.
27. Bulmer DM, Ali MS, Brownlee IA, Detmar PW, Pearson JP. Laryngeal mucosa: its susceptibility to damage by acid and pepsin. Laryngoscope. 2010;120:777–82.
28. Lechien JR, Saussez S, Karkos PD. Laryngopharyngeal reflux disease: clinical presentation, diagnosis and therapeutic challenges in 2018. Curr Opin Otolaryngol Head Neck Surg. 2018;26(6):392–402. https://doi.org/10.1097/MOO.0000000000000486.
29. Carroll TL, Fedore LW, Aldahlawi MD. pH impedance and high-resolution manometry in laryngopharyngeal reflux disease high-dose proton pump inhibitor failures. Laryngoscope. 2012;122(11):2473–81.
30. Fass R. Proton-pump inhibitor therapy in patients with gastro-oesophageal reflex disease: putative mechanisms of failure. Drugs. 2007;67(11):1521–30.
31. Ayazi S, Hagen JA, Zehetner J, et al. The value of high-resolution manometry in the assessment of the resting characteristics of the lower esophageal sphincter. J Gastrointest Surg. 2009;13:2113.
32. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun. 2015;36:625–30.