Laryngopharyngeal reflux: More questions than answers

ABSTRACT

Laryngopharyngeal reflux (LPR), an extraesophageal variant of gastroesophageal reflux disease, is associated with hoarseness, chronic cough, throat-clearing, sore throat, and dysphagia. But because these symptoms are nonspecific, laryngoscopy is often done and the diagnosis of LPR is considered if edema, erythema, ventricular obliteration, pseudosulcus, or postcricoid hyperplasia is noted. Most patients with suspected LPR are given a 2-month trial of a proton pump inhibitor. Yet there is still little or no solid evidence on which to base the diagnosis or the treatment of LPR. We review the current understanding of the pathophysiology and discuss current diagnostic tests and treatment regimens in patients with suspected LPR.

KEY POINTS

Laryngoscopy has high interrater variability, and results of pH monitoring do not reliably predict who will respond to treatment.

A proton pump inhibitor twice daily for 2 months is currently recommended for patients with laryngeal signs and symptoms. If the condition responds to therapy, tapering to once-daily therapy and then to minimal acid-suppression to control symptoms is prudent.

Patients whose symptoms do not respond to a proton pump inhibitor are unlikely to benefit from surgery. Other diagnoses should be entertained, while the drug is tapered to prevent rebound acid reflux.

THE PATHOPHYSIOLOGY OF LPR IS POORLY UNDERSTOOD

Transient relaxation of the lower esophageal sphincter

In a study in 10 healthy volunteers, Dent et al found that the pressure in the lower esophageal sphincter varies considerably over a 12-hour period. Episodes of reflux were not related to low basal (resting) pressure. Rather, 70% to 100% of reflux episodes occurred during random episodes of transient, complete, and...
inappropriate relaxation of the sphincter that lasted about 5 to 30 seconds. The mechanism of this relaxation is not known but is thought to be related to activation of the vagus nerve, possibly as a consequence of gastric distention.8

Gastric, not duodenal products seem to cause the damage
In a study in dogs, Adhami et al9 evaluated the possible role of gastric juices (acid and pepsin) vs duodenal juices (bile acids and trypsin) in laryngeal tissue damage. After taking baseline biopsy samples of the larynx, the investigators applied a variety of gastric and duodenal enzymes at varying pH levels (pH 1–7) to the larynxes. After 9 to 12 applications, they took another biopsy and assessed the changes visually and histologically.

At low (ie, acidic) pH levels, pepsin and conjugated bile acids were the most injurious, causing erythema and histologic evidence of inflammation. The authors concluded that gastric and not duodenal substances cause laryngeal injury and that acid-suppressive therapy “should eliminate the injurious potential” of acid reflux.9

The larynx is more sensitive than the esophagus
Monitoring of esophageal pH has shown that healthy people can tolerate as many as 50 episodes a day of acid reflux (pH < 4) in the esophagus. However, Koufman10 found that as few as three episodes of laryngeal reflux per week can cause severe laryngeal inflammation and injury.

Does pepsin deplete buffers, worsening acid damage?
Johnston et al11 took biopsies from a control group of healthy volunteers and from patients diagnosed with LPR. They detected pepsin in the samples from eight of the nine patients with LPR but in none of the controls. Furthermore, the tissue from patients with LPR had low levels of carbonic anhydrase III. The authors hypothesized that pepsin depletes the laryngopharynx of carbonic anhydrase III, and that therefore these tissues cannot produce enough bicarbonate to buffer the gastric acid. Less bicarbonate would mean greater acidity, so the pepsin would remain active and would be more likely to cause cellular damage.11

However, this contention is controversial. What is universally agreed upon is that reflux of gastric or gastroduodenal contents is most likely causing injury, most likely through direct exposure, although indirect effects through vagal mechanisms cannot be ruled out.

### CURRENT DIAGNOSTIC TESTS FOR LPR HAVE SHORTCOMINGS

The diagnosis of LPR has become more common over the last few years,4 and by some estimates up to 10% of patients presenting to ear-nose-throat physicians have complaints related to GERD.12 However, current diagnostic tests for reflux and LPR have many shortcomings and can lead to misdiagnosis of this disease (Table 2).

A careful history is important. Many patients report they have sore throat, hoarseness, cough, dysphagia, or chronic throat-clearing.13 Factors that may predispose a patient to esophageal reflux should be discussed, eg:

- Tobacco use
- Diet (eg, soda, spicy foods, fatty foods)
- Alcohol use
- Certain drugs (calcium channel blockers, nitrates, steroids).

Up to 50% of patients presenting with extraesophageal symptoms may not have classic reflux symptoms such as heartburn and regur-

### Table 1

**Symptoms often attributed to laryngopharyngeal reflux**

- Hoarseness
- Dysphonia
- Sore or burning throat
- Excessive throat-clearing
- Chronic cough
- Globus pharyngeus
- Dysphagia
- Postnasal drip
- Laryngospasm

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Key features of LPR: chronic hoarseness, cough, throat-clearing, sore throat, dysphagia, globus pharyngeus
TABLE 2

Advantages and disadvantages of tests for reflux

<table>
<thead>
<tr>
<th>TEST</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
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<tbody>
<tr>
<td>Endoscopy</td>
<td>Easy visualization of mucosal damage and erosions</td>
<td>Poor sensitivity, specificity, positive predictive value</td>
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<td></td>
<td></td>
<td>Requires sedation</td>
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<td></td>
<td>High cost</td>
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<tr>
<td>Laryngoscopy</td>
<td>No sedation required</td>
<td>No specific laryngeal signs for reflux</td>
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<td></td>
<td>Direct visualization of the larynx and laryngeal pathology</td>
<td>High interrater variability</td>
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<td></td>
<td>May contribute to overdiagnosis of reflux</td>
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<tr>
<td>pH monitoring</td>
<td>Easy to perform</td>
<td>Catheter-based, may have up to 30% rate of false negatives</td>
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<tr>
<td></td>
<td>Relatively noninvasive</td>
<td>Wireless system (Bravo) is costly</td>
</tr>
<tr>
<td></td>
<td>Prolonged monitoring</td>
<td>No pH predictors of treatment response in laryngopharyngeal reflux (LPR)</td>
</tr>
<tr>
<td></td>
<td>Ambulatory</td>
<td></td>
</tr>
<tr>
<td>Bilirubin monitoring</td>
<td>Easy to perform</td>
<td>Current design underestimates reflux by about 30% in acidic medium (pH &lt; 3.5)</td>
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<tr>
<td></td>
<td>Relatively noninvasive</td>
<td>Requires modified diet</td>
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<tr>
<td></td>
<td>Prolonged monitoring</td>
<td>Does not detect acid</td>
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<tr>
<td></td>
<td>Ambulatory</td>
<td>Not studied in LPR</td>
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<tr>
<td></td>
<td>Good correlation with gastric bile acid concentrations</td>
<td></td>
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<tr>
<td>Impedance monitoring</td>
<td>Easy to perform</td>
<td>Catheter-based</td>
</tr>
<tr>
<td></td>
<td>Relatively noninvasive</td>
<td>False-negative rate unknown but most likely similar to catheter-based pH monitoring</td>
</tr>
<tr>
<td></td>
<td>Prolonged monitoring</td>
<td>Unknown clinical relevance when abnormal on proton pump inhibitor therapy</td>
</tr>
<tr>
<td></td>
<td>Ambulatory</td>
<td>Unknown importance in LPR</td>
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<tr>
<td></td>
<td>Measures acidic and nonacidic gas and liquid reflux (combined with pH)</td>
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</tr>
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Laryngoscopy is nonspecific and subjective

Because the key symptoms of LPR are nonspecific, many patients who present to an otolaryngologist undergo laryngoscopy, mainly to rule out malignancy. Once cancer is ruled out, many patients are given a diagnosis of LPR.

Laryngoscopic findings often imputed to LPR (Figure 1) include erythema, edema, ventricular obliteration, postcricoid hyperplasia, and pseudosulcus.4 Of these, edema was the finding most often used to diagnose LPR in one analysis.15 However, Milstein et al16 discovered at least one sign of laryngeal tissue irritation in 80% to 90% of patients tested who did not have a history of an ear-nose-throat complaint or a diagnosis of GERD.

Furthermore, Branski et al17 performed transoral rigid laryngoscopy with videorecording in 100 consecutive patients presenting...
Laryngopharyngeal reflux: A challenging diagnosis

Patients with complaints such as sore throat, hoarseness, cough, dysphasia, chronic throat-clearing, and a feeling of a lump in the throat (globus pharyngeus) often undergo laryngoscopy to rule out malignancy and to evaluate for signs of tissue irritation. Once malignancy is ruled out, many patients receive a diagnosis of laryngopharyngeal reflux (LPR).

Signs on laryngoscopy

Laryngoscopic signs such as erythema (arrow), edema, ventricular obliteration, postcricoid hyperplasia, and pseuod-sulcus can be used to diagnose LPR. However, the evidence linking these signs to clinical symptoms is not strong.
with a chief complaint of dysphonia. Five board-certified otolaryngologists individually viewed each recording, scored the degree of erythema and edema, and assessed the likelihood that LPR played a role in dysphonia and the severity of the LPR findings. The physicians’ ratings showed considerable interobserver variability. In other words, this study showed that laryngeal findings are often nonspecific and that the laryngoscopic diagnosis of LPR tends to be subjective.17

The Reflux Finding Score. Concerned by the lack of consistency in the diagnosis of LPR, Belafsky et al18 created a scoring system for documenting the physical findings and severity of disease on a standardized scale. Their Reflux Finding Score is based on eight laryngoscopic findings: subglottic edema, ventricular edema, erythema, vocal cord edema, diffuse laryngeal edema, hypertrophy of the posterior commissure, granuloma or granulation tissue, and thick endolaryngeal mucus. The total score can range from 0 (best) to 26 (worst).

In 40 patients with LPR confirmed by pH monitoring, the mean score was 11.5, compared with 5.2 in 40 age-matched controls. The authors calculated they could be 95% certain that a person with a score higher than 7 has LPR.18

However, this diagnostic method has not been validated in a large-scale randomized trial and so has yet to be incorporated into routine otolaryngology practice.

Ambulatory pH monitoring is not so golden for diagnosing LPR

Although pH monitoring was once the gold standard for diagnosing reflux, it has since been shown to be unreliable in patients who have laryngeal symptoms.4

How high or low in the esophagus the probe is placed is clearly critical for useful results.4 But the test is subject to variability: different physicians place the probe in different locations, and the probe may shift. Another problem is that reflux may occur during untested periods.19

A pH of less than 4 in the esophagus had originally been shown to have high sensitivity and specificity,22 but Reichel and Issing21 suggested using a pH of less than 5 as the cutoff, which would identify more patients as hav-
most prevalent complaint in the study group was cough (56%), followed by heartburn (18%) and sore throat (10%).

Of the 39 patients, 25 (64%) had normal results on impedance/pH monitoring while on therapy, ruling out reflux. On pH monitoring off therapy, 28 (72%) of the 39 patients had abnormal results; this group included 13 (93%) of the 14 patients who had abnormal results on impedance/pH monitoring while on therapy. The authors recommended on-therapy testing with impedance monitoring in patients with refractory reflux, since it provides more useful clinical information. If the results of impedance/pH monitoring are negative in these patients, a diagnosis other than reflux should be considered.

**EMPIRIC PPI TREATMENT HAS SHOWN DISAPPOINTING RESULTS**

Because laryngoscopy and pH monitoring are not very sensitive or specific for LPR, experts recommend empiric therapy with a PPI twice daily. However, the results have been disappointing when PPIs were compared with placebo in clinical trials.

In a randomized controlled trial, we found that patients who had complaints of chronic throat-clearing, cough, globus, sore throat, and hoarseness had a similar response to twice-daily esomeprazole (Nexium) compared with placebo: their primary symptom had resolved by 16 weeks in 14.7% of the esomeprazole group vs 16.0% of the placebo group (P = .799). Similarly, the final findings on laryngoscopy such as edema, erythema, and surface irregularity were not significantly different between groups.

In addition, a meta-analysis of randomized controlled trials of PPIs for suspected GERD-related chronic laryngitis also had disappointing results (FIGURE 2). In this study, Qadeer et al analyzed eight trials with a total of 344 patients (195 on a PPI, 149 on placebo). In five of the trials, PPI therapy was superior to placebo in terms of the proportion of patients who had more than a 50% reduction in self-reported laryngeal symptoms, although the difference was statistically significant in only one of them. In the other three studies, more patients responded to placebo than to a PPI. When data from all eight trials were pooled, there was no significant difference between a PPI and placebo (risk ratio 1.28, confidence interval 0.94–1.74). The absolute rate of response to PPIs was 50%, vs 41% for placebo.

**Adding a histamine-2 receptor antagonist is not recommended**

Adding a histamine-2 receptor antagonist to PPI therapy has also been considered as a treatment for LPR.

Fackler et al studied 16 GERD patients and 18 healthy volunteers to determine if adding ranitidine (Pepcid) to the PPI omeprazole (Prilosec) could improve GERD symptoms. Patients underwent baseline manometry and then gastroesophageal pH monitoring before
starting the drugs. They first received omeprazole 20 mg twice daily alone for 2 weeks, and then added ranitidine 300 mg at bedtime. A pH test was done again after the first day of treatment with ranitidine, at the end of 1 week of combination therapy, and after 4 weeks of combination therapy. The combination reduced nocturnal acid breakthrough on day 1; however, due to tolerance to ranitidine, no significant difference in acid suppression was seen after 1 week of therapy. Therefore, this combination is not recommended.

**Surgery is not recommended either**

Some experts have argued for surgical fundoplication in patients whose symptoms persist despite drug therapy. Swoger et al\(^3\) treated 72 patients who had symptoms consistent with LPR with a PPI for 4 months; 25 patients in this group had less than a 50% improvement despite maximal drug therapy. Ten of these patients underwent surgical fundoplication, and 15 remained on drug therapy alone. At 1 year of follow-up, only one surgical patient (10%) reported improvement in laryngeal symptoms.

In view of this report and prior studies of surgical fundoplication,\(^4\) surgery is not recommended for patients whose symptoms do not respond to aggressive PPI therapy.

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