Chronic Hoarseness Secondary to Gastroesophageal Reflux Disease: Documentation with 24-H Ambulatory pH Monitoring


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Gastroesophageal reflux (GER) has been implicated in otolaryngologic problems, particularly chronic hoarseness that cannot be attributed to other causes. To study this relationship, we used 24-h ambulatory intraesophageal or dual pharyngoesophageal pH monitoring in 33 patients with chronic hoarseness and laryngeal lesions suggestive of acid irritation. Twenty-six of the patients (78.8%) had pH evidence of severe GER, being at least three times greater than the upper limit of normal. In contrast to 19 patients with proven esophagitis, this GER was worse in the upright position. Of 15 patients with both pharyngeal and esophageal probes, three had esophagopharyngeal reflux, and two had atypical unexplained pharyngeal decreases in pH to below 4.0. Less than half of the 33 patients had the typical symptoms of GER, and standard esophageal tests usually yielded normal findings. Occult GER, predominantly in the upright position, appears to be common and severe in patients with chronic hoarseness, who have laryngeal lesions suggestive of GER. The causative mechanisms are not clear. The 24-h esophageal pH monitor is useful in screening this potentially treatable problem.

INTRODUCTION

For years, laryngeal and pharyngeal signs and symptoms have been attributed to gastroesophageal reflux (GER) by many physicians, particularly otolaryngologists. Symptoms attributed to reflux include chronic cough (1–5), hoarseness (2, 4–6), throat clearing (3–6), and globus (2–9). Structural abnormalities that have been linked loosely to GER include head and neck granulomas (4, 5, 10–12), laryngeal edema with erythema (4, 5, 7, 13), laryngeal stenosis (11, 14, 15), contact vocal cord ulcers (4, 5, 10), and laryngeal cancer (5, 16). However, a causal relationship has not been confirmed, and there is no objective documentation of the nature or severity of the acid reflux patterns in such instances. We studied a group of patients referred from the Otolaryngology Section for esophageal pH monitoring because of the clinical suspicion that the chronic hoarseness and laryngeal lesions were secondary to GER. Twenty-four hour esophageal, and in many cases esophagopharyngeal, pH-monitoring studies were done in these patients in order to document, quantify, and characterize the association between otolaryngologic syndromes and GER in an attempt to clarify their pathophysiologic mechanisms.

METHODS

Patients

Thirty-three patients with chronic hoarseness referred to the Gastroenterology Section from the Otolaryngology Section were studied. The mean age of the 17 male and 16 female patients was 50 yr (range, 25–70 yr). The otolaryngologic evaluation was performed by one staff otolaryngologist (JAK). Every consecutive patient with hoarseness of chronic nature (greater than 3-month duration), not responsive to conventional therapy and with recurrent laryngoscopic findings suggestive of GER-related disease, was referred. There were three subgroups of patients: those with recurrent in situ carcinoma of the larynx (n = 7), those with subglottic stenosis (n = 5), and those with recurrent irritative findings (“reflux laryngitis”) such as erythema, edema, ulceration, granulation (n = 21). Of the latter group, 13 patients had inflammatory findings only, and eight had granulomas. The selection criteria for referral are presented in Table 1. There were only nine smokers in the study group; five had laryngeal carcinoma.

History

The patients answered a series of questions about esophageal symptoms (e.g., heartburn, regurgitation, dysphagia, substantial pain), otolaryngologic symptoms (e.g., hoarseness, globus, cough, choking episodes), and history of smoking, voice usage, and previous surgical or laser therapy of the upper gastrointestinal tract or head and neck area. All of these questions were asked by one investigator (GIW).
Manometric studies

After an overnight fast, esophageal manometry was performed with a low-compliance pneumohydraulic perfusion system, as previously described (17). Upper and lower esophageal sphincter (UES and LES) pressures and locations were established using a slow pull-through technique.

pH monitoring

Twenty-four-hour ambulatory esophageal pH monitoring was performed with any one of three monitors (Sandhill RMS, Oxford Medilog 100, or Delmar 706) that have been shown to give similar results (18). The pH probes used were Sandhill P-32-Konigsberg antimony probe and the Microelectrode MI-506. The esophageal probe tip was passed transnasally and located manometrically 5 cm above the LES. The presence of gastric acid was documented by advancing the probe until pH readings were less than 2.5, and then withdrawing the probe to the monitoring position. The last 15 patients studied had dual pharyngealpH monitoring. The pharyngeal probe (Sandhill Pediatric Probe) was “piggy-backed” onto the esophageal probe, and positioned 2 cm above the UES. This location was near the laryngeal inlet (Fig. 1). The distance between the two probes was measured and reconfirmed at the end of each study to insure that the pharyngeal probe had not migrated.

Patients were instructed to abstain from all drugs, especially those affecting gastrointestinal motility and gastric acid, for at least 16 h before the test. During the test, all were asked to abstain from those drugs, as well as from smoking, to consume only foods with pH >5, to drink no carbonated beverages, and to restrict milk, coffee, and tea consumption to mealtimes only. Using an event marker, the patient recorded on the monitoring apparatus meal times, bed and rising times, and any GER, otolaryngologic, or respiratory symptoms that occurred.

A drop in pH to less than 4.0 was considered evidence of GER (19). The pH variables studied were those proposed by Johnson and DeMeester: the percentage of time when the esophageal pH was less than 4.0, the number of episodes per hour with pH less than 4.0 that lasted for longer than 5 min, the total number of GER episodes per hour, and the longest duration of a GER episode (19). Each of these values was calculated for total time, time in the supine position, and time in the upright position. All tracings were inspected by one investigator (GJW) to confirm the computerized calculations, to correlate esophageal and pharyngeal pH tracings, and to insure the quality of recording. The esophageal 24-h pH study was considered abnormal if the pH variables exceeded two standard deviations from the mean derived from 20 asymptomatic normal subjects previously studied in our laboratory (mean age 30.1, range: 22–50 yr) (18). A pharyngeal reflux episode with pH less than 4.0 was considered secondary to GER if it was associated with an esophageal reflux episode, but such episodes occurring within 15 min of the end of a meal were excluded. These criteria for pharyngeal reflux were based on findings in a group of 12 asymptomatic volunteers (nine male, three female; mean age 31 yr), who showed no decreases in pharyngeal pH below 4.0 in association with episodes of esophageal reflux (20). The results from pH monitoring in these

<table>
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<th>TABLE 1</th>
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<td>Selection Criteria by Diagnostic Subgroup: Laryngoscopic and Clinical Aspects of Patient's Profile that Raise Suspicion of GER-Related Disease</td>
</tr>
</tbody>
</table>

**Group I. Carcinoma of the larynx**

A. Patients with skip-areas or widespread mucosal involvement with carcinoma in situ or microinvasive cancer (with or without a history of reflux)

B. Patients who developed granulomas or stenosis after treatment of laryngeal cancer

C. Nonsmokers with cancer of the larynx

**Group II. Subglottic stenosis**

A. Patients who do not respond to conventional treatment

B. Patients with a strong history of reflux (symptoms)

C. Patients with associated chronic unexplained cough and nocturnal chocking episodes

**Group III. Reflux laryngitis**

A. Patients with posterior laryngeal erythema and edema with thickening of posterior commissure mucosa

B. Patients with diffuse laryngeal edema and erythema

C. Patients with laryngeal granulomas
33 patients were compared with those in a group of patients of similar age with endoscopic evidence of esophagitis (10 male, 9 female, average age 44.2).

Other test for GER

Results of other esophageal tests, when available, were evaluated. These included esophageal manometry (n = 22), Bernstein test (n = 10), endoscopy (n = 11), and barium esophagography with double contrast (n = 13). A positive Bernstein test consisted of the reproduction of heartburn or chest pain with esophageal infusion of 0.1 N HCl, which disappeared with the infusion of normal saline. The endoscopic diagnosis of esophagitis was based on the presence of erosions, ulcerations, or Barrett’s epithelium. Careful attention was paid to ruling out the presence of ectopic gastric mucosa in the cervical esophagus (i.e., inlet patch). Esophagitis on the barium esophagogram was identified by the presence of thickened longitudinal folds, ulcerated or eroded esophageal mucosa, nonmalignant stricture, or any combination of those (21).

Statistics

The significance of the GER variables between healthy controls, esophagitis patients, and the study patients was assessed by unpaired Student’s t test and the Mann-Whitney U test.

RESULTS

Twenty-six of the 33 patients (78.8%) had abnormal 24-h pH monitoring results, and the mean reflux value in all categories measured was significantly greater than the normal control group (Table 2). Twenty-one (80.1%) of the 26 patients had an abnormal percentage of time with pH less than 4.0 (i.e., GER) in the upright position. Only upright values were obtained in one patient due to malfunction of the probe. Of the 25 patients studied for the full 24 h, 22 (88%) had abnormal reflux over the total period, and only 15 of those 25 (60%) patients had abnormal pH when recumbent. Ten patients had both upright and recumbent reflux (Table 2). When our study patients were compared with 19 patients with proven esophagitis seen on the Gastroenterology Service (Fig. 2), all pH variables were similarly abnormal, except that GER was significantly worse (p < 0.05) for our study patients when in the upright position (% time with pH < 4.0 and longest episode). Hoarse patients had documented acid reflux an average of 12.5% of the total study time, i.e., 3 h out of the 24-h period. In addition, they had markedly prolonged periods of acid exposure, suggesting poor clearance of acid. This slow clearance was particularly striking when upright reflux was evaluated, with the mean longest episode of GER being 26.5 min.

Twelve of the 15 patients who underwent dual pH monitoring had abnormal esophageal pH studies. Three

![Graph showing distribution of time with pH < 4.0](image)

**Fig. 2. Differences in GER measured at % time with pH <4 among patients with chronic hoarseness, esophagitis, and normals.

<table>
<thead>
<tr>
<th>pH Variables</th>
<th>Hoarseness Patients (n = 26)†‡</th>
<th>Healthy Controls (n = 20)‡</th>
<th>Esophagitis Patients (n = 19)‡</th>
<th>Normal Values‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time pH &lt; 4.0 upright</td>
<td>12.5 ± 2.0</td>
<td>1.7 ± 0.46§</td>
<td>7.9 ± 1.2*</td>
<td>&lt;5.85</td>
</tr>
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<td>% time pH &lt; 4.0 supine</td>
<td>9.1 ± 2.1</td>
<td>0.35 ± 0.16§</td>
<td>12.3 ± 2.7</td>
<td>&lt;1.81</td>
</tr>
<tr>
<td>% time pH &lt; 4.0 total</td>
<td>11.2 ± 1.7</td>
<td>1.3 ± 0.35§</td>
<td>9.8 ± 1.5</td>
<td>&lt;4.39</td>
</tr>
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<td>Episodes &gt; 5 min/h upright</td>
<td>0.5 ± 0.2</td>
<td>0.04 ± 0.2*</td>
<td>0.2 ± 0.1</td>
<td>&lt;0.22</td>
</tr>
<tr>
<td>Episodes &gt; 5 min/h supine</td>
<td>0.4 ± 0.02</td>
<td>0.01 ± 0.01*</td>
<td>0.2 ± 0.0</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>Longest upright episode in min</td>
<td>26.5 ± 5.2</td>
<td>4.2 ± 1.4*</td>
<td>11.1 ± 2.5*</td>
<td>&lt;16.77</td>
</tr>
<tr>
<td>Longest supine episodes in min</td>
<td>19.8 ± 5.1</td>
<td>1.1 ± 0.5§</td>
<td>29.1 ± 7.3</td>
<td>&lt;5.61</td>
</tr>
<tr>
<td>Episodes/h upright</td>
<td>3.6 ± 0.9</td>
<td>1.0 ± 0.02*</td>
<td>3.0 ± 0.4</td>
<td>&lt;2.49</td>
</tr>
<tr>
<td>Episodes/h supine</td>
<td>2.0 ± 0.7</td>
<td>0.2 ± 0.2*</td>
<td>1.2 ± 0.3</td>
<td>&lt;1.99</td>
</tr>
<tr>
<td>Total no. of episodes</td>
<td>59.3 ± 23</td>
<td>18.3 ± 3.6*</td>
<td>53.6 ± 17</td>
<td>&lt;51.1</td>
</tr>
</tbody>
</table>

* Values are mean ± SE.
† One patient had recordings only in the upright position.
‡ < mean ± 2 SD of control group.
§ p < 0.01 compared with hoarse patients.
§§ p < 0.05 compared with hoarse patients.
of these patients also showed definite pharyngeal reflux (1, 2, and 12 episodes, lasting 18 s to 46 min). In these three patients, the pharyngeal tracing was similar to the typical esophageal tracing, showing rapid falls in pH with gradual returns to baseline (Fig. 3). Among the remaining patients with dual pH recordings, two (one with normal and one with abnormal esophageal pH studies) had isolated decreases in pharyngeal pH to below 4.0 without concomitant episodes of esophageal acid reflux (Fig. 4). These pharyngeal episodes occurred between midnight and 6 AM, when the patients were recumbent. Finally, two other patients with abnormal esophageal studies also had isolated episodes of decreased pharyngeal pH, but the pH values were greater than 4.0 (4.4 and 4.8). Pharyngeal tracings from these four patients differed from the typical esophageal and pharyngeal reflux tracing, in that the pH decreased gradually and then rose rapidly to baseline (Fig. 4). This pattern was reproduced in two healthy volunteers in whom the probe was attached overnight to the buccal aspect of their molars. We have used the term “pharyngeal pseudoreflux” to describe these isolated and atypical decreases in pharyngeal pH.

The chief complaint of the 26 patients with abnormal GER was hoarseness (n = 22), hoarseness and chest pain (n = 2), hoarseness plus cough (n = 1), and hoarseness plus choking (n = 1). Only two patients complained spontaneously of possible esophageal symptoms (chest pain). When they were questioned more carefully about specific symptoms, heartburn had occurred in 14, regurgitation in 12 (all had heartburn also), chronic cough in five, chest pain in five, choking in five, globus or dysphagia in three, and sporadic abrupt episodes of dyspnea in eight (five of whom were nonsmokers).

Of the patients who had other esophageal studies, only approximately one-third of those with abnormal GER by 24-h pH testing had evidence of esophagitis (endoscopic: 3/11; radiographic: 5/13) or a positive Bernstein test (3/10).

**DISCUSSION**

The association between GER and laryngeal or pharyngeal disease has been suspected for many years, but is only briefly mentioned in the standard textbooks on gastrointestinal diseases (22). Previous studies in patients with otolaryngologic symptoms used the acid barium meal (3, 7) or fluoroscopy (2, 10, 14) to document GER, but these tests have a low sensitivity and specificity. By using the more sensitive ambulatory 24-h esophageal pH monitor, our study confirms and
accurately identifies the high prevalence and characteristics of GER in adult patients of this type. Our patients came from a select referral population, all with refractory hoarseness and specific laryngeal signs suggestive of GER. In this type of patient, the high percentage of abnormal 24-h pH studies and the magnitude of the deviation from normal of the GER variables are remarkable. The upright pattern of reflux seems to differentiate patients with hoarseness and GER from symptomatic patients with esophagitis. The scarcity of symptoms or signs of esophagitis is a characteristic of these patients, and should not detract the clinician from pursuing a diagnosis of GER disease. Why these characteristics of esophagitis are absent is not clear, but it may relate to the predominance of upright, as opposed to supine, GER.

It is the laryngeal examination, not the classic symptoms of GER, that usually makes the otolaryngologist suspect acid injury to the larynx. These patients may have laryngeal granulomas, stenosis, cancer, or inflammation, all with specific features thought to be characteristic of laryngeal acid injury (Table 1). The posterior larynx is the area most often affected, probably due to positional and gravitational effects (4, 7, 14, 23). The causal relationship of these lesions with acid exposure is supported by canine studies in which similar lesions were reproduced by intermittent applications of gastric acid to the vocal cords or subglottic area, but not by applications of normal saline or saliva (12, 15). Along with the morphologic characteristics of these lesions, recurrence after palliative therapy, concomitant GER symptoms, and absence of a history of cigarette smoking seem to be suggestive of reflux laryngitis.

The specific role of gastric acid in the pathogenesis of hoarseness and other laryngeal symptoms in humans is not well understood. Cherry and Margulies (10) first reported the association between GER and laryngeal disease in 1968. Two schools of thought have since developed. The first postulates a vagally mediated reflex wherein the stimulus is acid at the lower esophagus and the response is chronic repetitive throat clearing and coughing, which can eventually lead to laryngeal lesions and symptoms (2-4, 24). The second postulates direct acid injury and is based on case reports (10, 14) and on animal studies where similar lesions were produced by applications of acid to the larynx (15). In our attempt to test the latter hypothesis, we developed a dual pH probe with a pharyngeal monitor to record whether gastric acid actually did reach the hypopharynx. Even though most patients had severe GER by esophageal pH monitoring, the number of episodes of reflux with concurrent esophageal and hypopharyngeal pH values of less than 4.0 was disappointing. It is possible that the pharyngeal probe does not often yield positive results because its sensitivity is decreased by the size of the hypopharynx, e.g., the acid aspiration could be in mi-
crodroplets not recorded by the pH probe, or upper airway mucus may interfere with the probe. The pharyngoesophageal pH probe failed to document a direct link between esophageal acid reflux and hypopharyngeal aspiration in most cases, possibly due to the low sensitivity of the system.

We have noted pharyngeal pseudoreflux in at least six patients and in two normal volunteers (20). The pharyngeal pseudoreflux pattern is puzzling, and is usually obtained with the subject recumbent and asleep. The pathophysiology of this pH pattern is not clear, but one possible explanation may be related to the bipolar properties of the equipment. Since the pharyngeal cavity is large and saliva production decreases at night, there is a possibility that the pharyngeal probe dries up, moves away from the mucosa, or both, therefore breaking the bipolar circuit. When the patient swallows and produces saliva, or turns over and places the pH probe in contact with the mucosa, the bipolar nature of the system is reestablished and the pH probe returns to its baseline recording value. Other possibilities are changes in the composition or bacterial content of saliva or artifact due to inherent properties of the probes and equipment. Whereas we believe that the pharyngeal pH probe can be a valuable tool in characterizing the pathophysiology of hypopharyngeal reflux, improved technology and methods (i.e., the use of a monopolar electrode or lower placement of the probe) are necessary before its value can be proved.

Of special interest is the fact that the severity of the GER noted in our patients was not proportional to the incidence of traditional symptoms (heartburn, chest pain) or signs (esophagitis) of GER disease. Traditional tests for GER were usually negative. The fact that patients with reflux laryngitis had GER predominantly in the upright position may help to explain this disparity. Due to the occult nature of GER, data obtained with the ambulatory 24-h intraesophageal pH probe comprise the currently accepted "gold standard" for the diagnosis of reflux. The data from our study help to emphasize that laryngeal symptoms with characteristic laryngeal lesions, particularly chronic hoarseness, may be secondary to occult GER. This specific subset of patients may benefit from a gastroenterologic evaluation, with particular emphasis on prolonged intraesophageal pH monitoring. Since chronic hoarseness is a common complaint, the incidence of occult GER without typical gastroesophageal symptoms and signs may be substantial, and at present, unrecognized by many physicians. With the advent of very effective treatment of GER disease, i.e., omeprazole (25), a well-designed placebo-controlled trial in this setting may be warranted.

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REFERENCES


