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Is Laryngopharyngeal Reflux Related to Functional Dysphonia?

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Objectives: Laryngopharyngeal reflux (LPR) may be a contributing factor in chronic hoarseness. The association of LPR with functional dysphonia (FD), the most common voice clinic diagnosis, is unknown. We attempted to determine whether patients with FD have a higher rate of laryngeal exposure to acidic stomach contents than do healthy volunteers.

Methods: We recruited through the voice clinic 23 patients who had had persistent dysphonia for 3 months. Pregnancy, major structural laryngeal abnormality, and vocal fold paralysis were exclusion criteria. Eight healthy volunteers were recruited. The subjects gave informed consent to enter the study, which had the approval of our hospital ethics committee. The patients and control subjects underwent 24-hour dual-probe pH-metry.

Results: Twenty-two patients and 6 control subjects completed the study. Overall, there seemed to be no statistical differences between patients and controls on all but 2 channel 1 pH-metry parameters. These were the longest reflux episode (seconds) in a supine position, and the fraction of time the pH was less than 4 in a supine position. Both of these time periods were longer in patients than in the controls ($p < .05$).

Conclusions: Our study demonstrated an association between LPR and FD for 2 pH parameters. Larger studies are required to assess the potential relationship between nonorganic dysphonias and reflux. Furthermore, the presence of a multifactorial causation of FD, including "medical" and psychological causes, should be addressed in future studies.

Key Words: dysphonia, hoarseness, laryngopharyngeal reflux.

INTRODUCTION

Functional dysphonia (FD) refers to impairment of voice production in the absence of mucosal or neurogenic disease of the larynx. It is a diagnosis of exclusion and is an enigmatic and controversial voice disorder that is frequently encountered in multidisciplinary voice clinics.[1,2] In 2 large studies by a North Carolina group, reflux was found, by means of pH monitoring, in 50% of dysphonic patients,[3,4] whereas in another study, as many as 40% of patients referred to a voice specialist were thought to have FD.[5] Because FD remains the most common diagnosis in a voice clinic and reflux has been found in more than half of dysphonic patients, we attempted to look for a possible relationship between laryngopharyngeal reflux (LPR) and FD.

MATERIALS AND METHODS

The aim of the study was to determine whether patients with FD have a significantly higher rate of laryngeal exposure to acidic stomach contents than healthy volunteers. We used 24-hour dual-probe ambulatory pH-metry to compare the prevalence of proximal reflux in a cohort of patients with FD with that in a control group. The dual probe was positioned in the esophagus under fiberoptic laryngoscopic visual control. By this technique, the proximal probe can accurately be positioned at the upper esophageal sphincter (UES). The distal probe allows confirmation that decreases in pH are directly related to acid reflux of stomach contents as opposed to ingested food or pseudoreflux. Then, 24-hour ambulatory pH-metry is performed while the subject goes about his or her normal daily routine.

To date, the most commonly used diagnostic test for LPR detection remains ambulatory 24-hour dual-probe pH monitoring.[6] Smit et al,[7] in 1998, described a relatively easy and reliable technique for the placement of the proximal probe without the use of manometry and established normal ranges for pH values at the level of the UES. This method has been used in our study.

Twenty-three patients (9 men and 14 women) were recruited from our voice clinic, Department of Otolaryngology and Speech Therapy at The Freeman Hospital, Newcastle Upon Tyne. Patients were considered to have FD if they had a history of persistent dysphonia for greater than 3 months and had

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no evidence of puberphonia, spasmodic dysphonia, or structural abnormality on videostroboscopy. All subjects gave written informed consent to enter the study, which had the approval of our hospital ethics committee. We included patients 21 to 73 years of age (mean, 43 years). We excluded pregnant patients and those with a major structural laryngeal abnormality (carcinoma, polyps, edema, or vocal fold paralysis). Minor degrees of laryngeal inflammation and mild nodule formation are not clearly distinguished from FD; therefore, patients with these disorders — typically referred for speech therapy — were included in our study. Eight healthy volunteers 23 to 40 years of age (mean, 33 years; 1 man and 7 women) were recruited from our hospital staff. Three were current cigarette smokers. The controls were only recruited if they reported no history of voice problems and demonstrated no structural or organic laryngeal disease on fiberoptic laryngoscopy. None were taking any medication at the time. All subjects underwent ambulatory 24-hour dual-probe pH monitoring, with 2 monocrystalline antimony pH probes positioned along a single catheter (diameter, 2.1 mm; probes 10 cm apart) and a cutaneous reference electrode. Both probes were calibrated for 5 minutes in buffer solutions of pH 7 and pH 1 before testing. The nose was sprayed with a local anesthetic and decongestant spray, and the catheter was passed transnasally under fiberoptic laryngoscopic visual control. The proximal probe was placed, under direct vision, just above the UES. The outer part of this tube was connected to a portable digital pH recorder (Digitrapper MK-II, Synectics Medical Inc, Irving, Texas), which the subjects carried throughout the 24-hour period. The patients went about their normal routine. While at home during the study, the subjects were instructed to take their normal diet, assume normal activities, and maintain a diary indicating activities, time of retiring, and time of rising in the morning. No restrictions were placed on cigarette smoking. The only dietary restrictions were avoidance of carbonated beverages and highly acidic foods (pH of less than 5). All subjects were asked to complete questionnaires relating to gastroesophageal reflux (GERD), dysphonia, vocal performance, and general health.[8-11]

After the 24-hour monitoring period, the probe was removed and the data were transferred to a computer for analysis. In addition, the pH recordings were displayed on a screen for a detailed manual analysis and determination of the relationship of pH declines registered at the 2 probe sites. For both sites, a decrease in pH below 4 that was not induced by eating or drinking was considered the beginning of a reflux episode, and the following rise to pH above 5 was considered the end of such an episode. To be accepted as a pharyngeal reflux event, the decrease at the pharyngeal probe had to be abrupt and simultaneous with the decrease in the esophagus, or preceded by a decrease in pH of similar or larger magnitude at the esophageal probe. Thus, acid episodes induced by oral intake, pharyngeal probe movement, or loss of mucosal contact in which the pharyngeal pH decline might precede esophageal pH drops were excluded as LPR episodes. For the analysis of results, we consider more than 4 reflux episodes to be pathological. A pH of less than 4 for more than 0.1% of the total time, 0.2% of the time upright, or 0% of time spent supine was also considered to be pathological.[7]

Our data did not fulfill the criteria for parametric tests, and, therefore, nonparametric tests were used on the 2 groups. The SPSS (version 12.0) statistical software (SPSS, Chicago, Illinois) was used for the analysis. A total of 24 parameters were compared between patients and controls. Channel 1 represents the proximal (pharyngeal) probe, and channel 2 the distal (esophageal) probe. The following 4 parameters were included in the analysis: number of reflux episodes, number of reflux episodes greater than 5 minutes, longest reflux episode, and fraction of time that the pH was less than 4. All 4 were calculated for the entire recording period (total), as well as for the upright and the supine positions. All of the above parameters were measured for both channels (channels 1 and 2), giving a total of 24 parameters (Table 1). The results are expressed as median (interquartile range [IQR]). The Mann-Whitney U test was used to compare differences between the patients and controls. The Wilcoxon signed rank test was used to compare paired (related) samples. A p value of less than .05 was considered to be statistically significant.

RESULTS

Thirty-one consecutive patients and controls underwent dual-probe 24-hour pH monitoring (23 patients and 8 healthy volunteers). Of the 23 patients, 1 patient did not tolerate the procedure, and the tube had to be removed less than 6 hours after successful insertion. Her results were not included in the analysis. In 2 of the volunteers, pH monitoring was not recorded because of system malfunctioning, and as a result, both were excluded from the study. In total, 22 patients and 6 healthy volunteers finished the study.

The median (IQR) total duration of pH recording for the entire group was 23.5 hours (23.4 to 23.55; Table 2). As expected, the patients spent a longer time in the upright position than in the supine posi-

TABLE 1. FINDINGS OF pH RECORDING

		Channel 1			Channel 2		
		Patients	*Controls*	*p*	*Patients*	*Controls*	*p*
No. of reflux episodes (any)	Total	20 (10-29.5)	14.5 (9.25-39.25)	.764	45.5 (23.25-91.5)	34 (22.75-57.5)	.460
	Upright	15 (7.5-29.25)	14.5 (9-36.25)	.892	36.5 (10.75-75.5)	32 (21-48)	.892
	Supine	1.5 (0-10)	0 (0-1.75)	.078	3.5 (1.75-9)	3 (0.75-8.75)	.682
No. of reflux episodes >5 min	Total	1 (0.75-6)	1 (0.75-3.25)	.764	3 (1-5.25)	3.5 (0.75-5)	.682
	Upright	1 (0-3)	1 (0.75-3.25)	.892	3 (1-5)	2.5 (0.75-4)	.427
	Supine	0 (0-1)	0	.194	0 (0-1)	0 (0-1.75)	.764
Longest reflux episode (s)	Total	10 (6-67.5)	6 (4-11.5)	.175	11 (7-24.75)	13.5 (7.25-61)	.604
	Upright	9 (3-57.25)	6 (4-11.5)	.365	11 (6.75-16)	10.5 (7.25-19.25)	.892
	Supine	1.5 (0-19)	0 (0-0.25)	.039*	1.5 (0-5.25)	1.5 (0-43)	.849
Fraction of time pH < 4 (%)	Total	2.15 (1.15-9.67)	2.6 (1.1-4.67)	.764	5.75 (3.1-8.72)	3.5 (0.75-5)	.978
	Upright	3.4 (1.4-9.1)	4.4 (1.625-6.55)	.935	8.45 (3.82-11.3)	2.5 (0.75-4)	.395
	Supine	0.5 (0-6.55)	0 (0-0.1)	.045*	0.6 (0.07-2.77)	0 (0-1.75)	.806

Results are expressed as median (interquartile range).

*Only 2 parameters, both in channel 1 — namely, longest reflux episode in supine position, and fraction of time pH was <4 in supine position — were statistically different between patients and controls ($p < .05$).

tion (14.46 hours [13.49 to 16.29] versus 9.07 hours [7.11 to 10.06]; $p < .001$, Wilcoxon signed rank test). The patients and volunteers had similar recording times in the upright and supine positions; however, the total duration of the recording was higher in the patient group.

The principal pH parameters as recorded by the proximal (channel 1) and distal (channel 2) probes in the 28 study participants are presented in Table 3. According to the pH-metry criteria set in Materials and Methods, all 22 patients and the 6 volunteers had values in keeping with LPR. The fraction of time in total that the pH was less than 4 at the proximal probe (channel 1) was in excess of 0.1% in all patients and volunteers (Table 3). The median fraction of time (IQR) during which the pH was less than 4 was 2.15% (1.15% to 9.67%) for the 22 patients and 2.6% (1.1% to 4.67%) for the 6 volunteers. Furthermore, given that LPR was defined as more than 4 reflux episodes, all but 2 patients (patients 7 and 18) and 1 volunteer (number 25) were found to have pathological values at the proximal probe.

Comparisons between patients and volunteers are summarized in Table 4. As expected, the patients had a worse performance on the Vocal Performance Questionnaire than did the volunteers (median [IQR] score, 29 [25.5 to 37.5] versus 10 [10 to 10.5]; $p < .001$). Similarly, on the GERD questionnaire (Harmony I-684 Symptom and Lifestyle Questionnaire), the patients had a worse performance than the volunteers, both in total and on all 3 parts of the questionnaire (Table 4). Finally, no statistical differences were encountered on the General Health Questionnaire–12 scores between patients and volunteers.

TABLE 2. DURATION (HOURS) OF pH RECORDING FOR PATIENTS, VOLUNTEERS, AND ENTIRE GROUP

pH Recording Time	*Patients*	*Volunteers*	*Total Population*
Total duration	23.5 (23.4-23.55)	23.33 (23.05-23.51)	23.5 (23.4-23.55)
Upright position	14.46 (13.49-16.29)	14.3 (13.18-15.36)	14.46 (13.37-16.22)
Supine position	9.07 (7.11-10.06)	8.95 (7.8-10.15)	9.07 (7.19-10.09)

Values are expressed as median (interquartile range).

Overall, there was a statistical difference between patients and volunteers on 2 channel 1 pH-metry parameters. These were the longest reflux episode in a supine position, and the fraction of time the pH was less than 4 in a supine position. Both of these time periods were longer in patients than in controls ($p < .05$).

DISCUSSION

The identification of LPR has increased exponentially over the past 10 years, to the point of overdiagnosis. Heartburn is acknowledged frequently to be absent, and any of the candidate symptoms may arise from additional, unrelated causes. Disappointingly, lower-esophageal ambulatory pH recording and dual-probe pH studies in the upper esophagus and pharynx have failed to generate a diagnostic gold standard.[12] There is a consensus that LPR occurs more in the upright than in the supine position and that fewer than 20% of patients have esophagitis.[13] As pH-metry results are insufficiently sensitive or specific, diagnosis is often made on the basis of an empirical trial of acid suppression by a proton pump inhibitor (PPI). But is overdiagnosis of LPR harmful? Patients may welcome the relief of associated gastroenterological symptoms, but the costs are

TABLE 3. pH-METRY RESULTS OF 28 STUDY PARTICIPANTS

Subject No.	No. of Reflux Episodes (Any) in Total*		No. of Reflux Episodes >5 Min in Total*		Fraction of Time pH < 4 (%) in Total*	
	Ch 1	Ch 2	Ch 1	Ch 2	Ch 1	Ch 2
1	26	25	9	1	20.9	1.6
2	24	35	7	7	32.9	17.5
3	63	14	18	4	33.5	2.8
4	6	126	0	5	2.0	9.4
5	15	56	1	4	1.0	5.2
6	34	63	1	5	2.3	6.9
7	4	4	2	2	1.0	1.0
8	18	18	1	1	1.2	1.2
9	90	90	7	7	20.7	20.7
10	10	34	0	6	0.6	6.7
11	28	44	1	3	5.5	8.5
12	11	12	6	7	5.3	10.3
13	71	113	3	3	5.1	6.1
14	9	29	3	1	6.0	3.2
15	117	103	6	3	30.3	3.9
16	16	46	1	2	1.6	4.1
17	19	96	0	2	1.2	7.9
18	3	10	0	0	0.1	1.0
19	28	81	0	1	1.3	6.6
20	10	60	1	6	0.8	5.4
21	21	45	1	1	1.8	3.6
22	28	135	1	5	2.8	12.9
23	11	55	1	5	7.0	23.4
24	12	19	1	1	1.4	2.3
25	4	24	0	0	0.2	1.0
26	17	65	1	5	1.4	8.2
27	40	29	4	4	3.9	7.0
28	39	39	3	3	3.8	3.8

First 22 subjects were patients (numbers 1 to 22), and remaining 6 (numbers 23 to 28) were healthy volunteers.

Ch — channel.

*In both upright and supine positions.

TABLE 4. QUESTIONNAIRE SCORE DIFFERENCES BETWEEN PATIENTS AND VOLUNTEERS

	Patients	Volunteers	p
Vocal Performance Questionnaire	29 (25.5-37.5)	10 (10-10.5)	<.001
Harmony I-684 Symptom and Lifestyle Questionnaire			
Part I: Symptom Questionnaire	5 (2-6.5)	0 (0-0)	<.001
Part II: Lifestyle Questionnaire	9 (3.5-13)	1 (0-2)	.007
Part III: GSRS Questionnaire	10 (4.5-14)	0 (0-0.5)	<.001
Total score	24 (9.5-34)	2 (0-2)	<.001
General Health Questionnaire–12	23 (21-25.5)	20 (15.75-23.25)	.065

Scores are expressed as median (interquartile range).

GSRS — Gastrointestinal Symptom Rating Scale.

considerable, and other, perhaps more effective, approaches may be overlooked.

Despite its weaknesses, dual-probe 24-hour pH monitoring remains the most commonly used test for LPR detection. The establishment of a normative database for LPR is controversial and ongoing and remains a topic of debate.

In our study we used the method and criteria suggested by Smit et al.[7] Their technique avoids the use of manometry, and it is relatively easy, reproducible, and cost-effective.[7] Other authors have used an alternative standard in which any LPR is defined as abnormal.[8] However, studies focused exclusively on establishing a normative database have shown that small amounts of LPR are present in asymptomatic patients.[12-15] The Winston-Salem group believes that manometry should always precede pH-metry, because not only does it accurately locate the upper and lower esophageal sphincters, but it also allows for evaluation of pharyngoesophageal function.[16]

The positioning of the proximal probe is also somewhat controversial. Loss of mucosal contact, probe displacement, pH changes caused by oral intake, and intermittent drying are a few of the problems blamed for spurious results.[17] The presence of the proximal probe in the posterior pharynx has been speculated to precipitate acid reflux secondary to irritation, possibly resulting in false-positive results.[17] The tendency for false-negative results has been as high as 20% to 50%. The best place for the proximal probe positioning should be as close as possible to the target organ, ie, the larynx, and should allow the probe to make permanent contact with the mucosa during the 24-hour period. Smit et al[7] found that with the proximal probe placed in the upper esophageal sphincter, only 5% of subjects (1 in 20) had proximal pH drops (pseudoreflux) in the supine position. Wiener et al[18] stated that pseudoreflux episodes are usually found in a recumbent and sleeping position. Postma et al,[16,19] on the other hand, believe that the proximal probe should be placed in the pharynx and not in the upper esophagus, as has been suggested by some.

The importance of the pharyngeal probe cannot be overemphasized. When the pharyngeal probe data are positive, they are thought to be diagnostic of LPR.[8] False-negative results can occur if we rely only on the esophageal (distal) probe, as Katz[20] showed in a small number of patients with LPR. The typical pattern of LPR is intermittent, and therefore, the diagnosis is not always easy, because a negative pH study does not necessarily rule out LPR.[21] Vaezi

et al[22] reported a significant day-to-day variability in acid exposure in the proximal esophagus.

One of the limitations of this study is the difficulty in choosing healthy volunteers and separating those who are healthy from those who require further investigation by means of the available questionnaires. Furthermore, the high population prevalence rate makes it hard to define the boundary between physiological gastroesophageal reflux and GERD. The assessment and quantification of changes in the full range of GERD symptoms on treatment is of increasing interest in clinical trials. Many physicians are skeptical of data derived from symptom questionnaires, and previous attempts to produce a GERD symptom scale have been time-consuming and have used heartburn as both a symptom and an inclusion criterion. Using heartburn as the sole criterion to categorize whether a patient has GERD is a major weakness of various studies, as heartburn may be absent in 25% of patients. In order to be scientifically accepted, a questionnaire has to fulfill standard criteria such as validity, responsiveness, and reliability as determined by well-established psychometric methods. The popular Reflux Symptom Index omits throat pain, and by including heartburn may induce a bias in therapy. In our study there were many cases of healthy volunteers who, despite normal Harmony I-684 scores, had an abnormal number of reflux episodes. This paradox may well reflect the fact that questionnaires in general are perhaps far from ideal in predicting reflux or in differentiating between healthy volunteers and subjects with reflux.

Another weakness of any study that deals with LPR is the lack of an objective diagnostic tool. Currently, diagnosis of suspected LPR is based on a combination of symptoms and findings of reflux laryngitis (with high scores on reflux symptom and sign questionnaires) together with abnormal pH results. Our patients with FD had most of the videolaryngoscopic findings of LPR. They all (except patient 18) had posterior erythema, ventricular obliteration, pseudosulcus, thick endolaryngeal mucus, posterior commissure hypertrophy, laryngeal edema, and granulations. These are "signs" widely thought to be reflux-related. Dual-probe pH-metry, although established for lower esophageal reflux, has not proved so helpful in LPR detection. Normal pH values at the distal esophagus have been well established in the literature. However, much controversy still surrounds what constitutes LPR. The criteria used to diagnose GERD do not apply in LPR, because baseline pH values for the hypopharynx are still unknown. Healthy asymptomatic volunteers may have wide-ranging values of acidification in the proximal esophagus, and therefore, extreme values are not unusual. In this series of 6 volunteers, the median fraction of time that the pH was less than 4 was 2.6% — slightly higher than the 1% value a previous study from the same group found (unpublished data). This finding is perhaps not surprising, given that distal esophageal pH-metry results also show a skewed distribution in which occasional healthy asymptomatic individuals show acid exposure times well above the median.

Finally, this is a study that uses pH-metry, an invasive test that is not very well tolerated. Because of the considerable reluctance to participate, recruitment of both patients and, particularly, volunteers was difficult. As a result, the study took a long time to complete and suffers from small numbers. Nevertheless, any study dealing with LPR, a very controversial topic, is bound to be flawed from its very beginning, as there is still no ideal diagnostic test and pH-metry, still the gold standard, is far from perfect.

Empiric antireflux treatment has been used in recent years as an alternative diagnostic method for LPR detection instead of dual-probe 24-hour pH monitoring. As the signs of reflux are at best nonspecific and at worst absent, response is based largely on reported improvement in symptoms. Therapeutic response to empiric therapy allows for both diagnosis and treatment of LPR and involves lifestyle modifications and the use of acid-suppressing medications — most recently, PPIs. In head and neck symptoms, most reports have been empirical, uncontrolled therapeutic trials of treatment with PPIs that have reported a positive effect, but the few negative placebo-controlled double-blind studies currently in the literature showed no significant difference between placebo and PPIs, suggesting that reflux laryngitis may be a self-limiting condition.[23]

CONCLUSIONS

Our study demonstrated an association between LPR and FD for 2 pH parameters. There are still many unanswered questions regarding both LPR and FD. The initial enthusiasm of the "believers" in reflux was replaced by much skepticism, mainly caused by the recent negative studies of LPR treatment (placebo versus PPIs). On the other hand, studies such as the one from Tasker et al[24] opened new horizons in the association between pepsin and common middle ear conditions. The role of this proteolytic enzyme in tissue damage caused by reflux is currently being addressed, and so are the complexity of the immunologic role of the laryngeal mucosa and the role of carbonic anhydrase in LPR. The search for an objective diagnostic tool, both clini-

cal, like the Reflux Symptom Index, and immunologic, will perhaps give answers to these questions. Clearly, cell biology holds the key to understanding reflux disease. With the recent findings about pepsin, the search is under way to find out how pepsin results in the development of reflux-related laryngeal disease.

As far as FD is concerned, there is increasing evidence that speech therapy is beneficial, and although a possible link was found between LPR and FD, larger studies are required. Furthermore, the presence of a multifactorial causation, including "medical" and psychological causes, should be addressed in future studies.

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