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Clinical and Acoustical Voice Quality Evolutions Throughout Empirical Treatment for Laryngopharyngeal Reflux Disease According to Gender: A Preliminary Study

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Keywords
Laryngopharyngeal · Reflux · Laryngitis · Voice · Gender

Abstract
Objective: To compare symptoms, signs, and acoustical voice quality changes throughout the 6-month course of empirical treatment between laryngopharyngeal reflux (LPR) males and females. ***Materials and Methods:*** Forty clinically diagnosed LPR females and 40 males with a reflux finding score (RFS) >7 and a reflux symptom index (RSI) >13 were treated with pantoprazole and diet recommendations during 3 or 6 months according to their evolution. RSI, RFS, and acoustic parameters were assessed at baseline and 3 and 6 months posttreatment. A correlation analysis between videolaryngostroboscopic findings and acoustic measurements was performed. ***Results:*** RSI, RFS, and many acoustic measurements (i.e., percent jitter, percent shimmer, phonatory fundamental frequency range, fundamental frequency variation, and peak-to-peak amplitude variation) significantly improved from baseline to 3 months posttreatment in male group. In female group, RSI and RFS total score significantly improved along the 3 first months of treatment. However, some clinical outcomes (i.e., RSI total score, hoarseness, cough, and globus) continued to improve from 3 to 6 months of treatment. We did not identify significant improvement of acoustic measurements in female group. The correlation study did not reveal significant correlation between videolaryngostroboscopic findings and acoustic measurements. ***Conclusion:*** This preliminary study suggests the occurrence of gender-related differences in the LPR therapeutic response. Further studies need to clarify whether females require a longer course of therapy than males.

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Introduction

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effect of gastroduodenal content reflux, which induces morphological changes in the upper aerodigestive tract [1]. A few American studies reported that LPR would affect 10% of outpatients of otolaryngology consultations [2] and >50% of patients in voice centers [3]. Among the most prevalent symptoms of LPR, hoarseness could involve >70% of LPR patients [1, 4] although the direct association between LPR and hoarseness is still debated with possible over-diagnosis in patients who did not benefit from pH monitoring [5]. The current LPR diagnosis is difficult given the lack of specificity of signs and symptoms, the lack of gold standard, and the high false-positive and false-negative rates of pH impedance metry [6, 7]. Moreover, with regard to the cost, and the unavailability of pH impedance metry in some centers, an increasing number of authors use empirical therapeutic trial as cost-effective diagnosis method [8, 9]. Thus, patients who significantly improve both LPR signs and symptoms after 3 or 6 months of treatment can be usually considered as LPR patients, while nonresponder patients require pH impedance metry to confirm the diagnosis [10]. In this approach, some clinical tools such as reflux symptom index (RSI) [9] and reflux finding score (RFS) [10] have been developed to assess the efficiency of treatment. Moreover, regarding the high prevalence of hoarseness, some recent studies showed that a multidimensional evaluation of voice quality can be used as therapeutic outcomes [1, 2]. Nowadays, although a few studies suggested that LPR females are more vulnerable to the development of both hoarseness and vocal fold lesions than males [11–13], no trial interested to the evolution of voice quality throughout treatment according to gender.

The aim of this study is to compare symptoms, signs, and voice quality changes throughout the 6-month course of empirical treatment between LPR males and females.

Materials and Methods

Subject Characteristics

From September 2013 to April 2016, 122 patients with LPR complaints were recruited from the Otolaryngology-Head & Neck Surgery Departments of EpiCURA and Liege Hospitals (Ethics Committee references: 2015/99 and B707201524621). The LPR diagnosis was based on both RSI >13 and RFS >7 according to the thresholds described by Belafsky et al. [9, 10], which were associated with a positive pH monitoring result. The exclusion factors and the flowchart of the study have been described in a previous publication [11]. Overall, exclusion factors included neurological disease affecting the voice, psychiatric illness, upper respiratory tract infections within the last month, antacid treatment (i.e., proton pump inhibitors [PPIs], alginate, antihistamine, or gastroprokinetic) already started at the diagnosis time, history of cervical surgery or radiotherapy, laryngeal trauma, vocal cord paralysis/paresis, muscle tension dysphonia, benign vocal fold lesions, pharyngolaryngeal malignancy, active allergies (skin prick tests), asthma, chronic obstructive pulmonary disease, rheumatologic inflammation diseases, PPI hypersensitivity, untreated thyroid disease, prior antireflux surgery, or chemical exposure causing laryngitis. Active smokers, alcoholics, and pregnant and lactating women were also excluded.

Patients were treated with diet and PPIs for 3 initial months (20 mg pantoprazole, twice-daily). After 3 months of treatment, a titration of PPIs was made for responder patients (RSI ≤13 and RFS ≤7) according to the current trend of empirical management of LPR patients [8–10]. The doses of nonresponder patients after 3 months of treatment have been increased (40 mg pantoprazole, twice daily) and they were clinically assessed a second time (6 months posttreatment). Patients were definitively considered as LPR patients in case of complete response to treatment (RSI ≤13 and RFS ≤7) at the end of the therapeutic period. Regarding recommendations [6, 8], the diagnosis of nonresponder patients (RSI >13 and/or RFS >7) was based on positive pH impedance metry result (occurrence of ≥1 proximal reflux episode at the pH impedance monitoring). We did not perform pH impedance monitoring at baseline for all patients because the technique was not available in our center. The diet recommendations were based on a dietary analysis of the habits of the patients and the administration of a validated grid of diet recommendations (Table 1). Adherence to diet was assessed by both the patient throughout the therapeutic course and the physician at the end of treatment with a point scale ranging from 0 (nonadherent) to 10 (fully adherent to the recommendations).

Clinical and Voice Quality Outcomes

Clinical and voice quality evaluations were conducted at baseline and 3 and 6 months after the start of treatment (Fig. 1). LPR findings and symptoms were respectively evaluated with the French version of RSI and RFS [14]. The videolaryngostroboscopic findings were rated by a senior laryngologist using videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) in a blind manner regarding the patient complaints (RSI). In other words, the laryngologist assessed RFS without knowing the symptoms of the patient and the related presence of LPR or not.

The following acoustic parameters were measured on the entire signal of the 3 sustained vowel/a/productions with MDVP® software (KayPentax®, NJ, USA): fundamental frequency (F0), highest F0 (Fhi), lowest F0 (Flo), SD of F0, fundamental frequency variation, jitter percent (Jitt), phonatory fundamental frequency range, shimmer percent, peak-to-peak amplitude variation, and noise-to-harmonic ratio. The microphone was placed at a distance of 30 cm from the mouth, and recordings were made in a sound-treated room.

To study the potential relationship between videolaryngostroboscopic findings and objective voice quality impairments, we conducted a correlation analysis between RFS items and acoustic measurements according to gender.

Table 1. Recommendation grid (diet and lifestyle modifications)

Lifestyle habits	Foods to favor	Foods to avoid
1. Stress control 2. Tobacco and other addiction(s) reduction 3. Reduction of size of meals 4. Hot lunch in place of hot dinner 5. Eat slowly 6. Do not talk while eating 7. Avoid tight clothing 8. If possible avoid the following drugs: *Non steroidal anti-inflammatory drugs* *Corticosteroids, aspirin, theophylline,* *Progesterone, iron supplementation,* *Calcium channel blockers*	1. Meat, fish, chicken, eggs Fresh and thin fish Shrimps, lobster, shellfish Chicken fillet (without skin) Turkey (without skin and fat) Duck (without skin and fat) Low-fat meat – *Veal cutlet, pork tenderloin* – *Rindless, fatless, cooked ham* – *Steak, fillet, striploin* – *Roast veal, veal chop, horse* Remove fat from meat Egg white Other:…….....	1. Meat, fish, chicken, eggs Fat fish, fish oil (sardines, cods, herrings) Fat chicken High-fat meat – *kidneys, bacon, ground meat* – *Pâté, tripes, lamb* – *Lamb chops, shoulder or legs of lamb* – *Ribs, rib steak* – *Pork chops, roast, and shoulder* – *Foie gras* Delis, sausage, salami Other:…….....
If heartburn 1. Reduction of overweight 2. Elevating the head of the bed	2. Dairy products Low-fat cheese Skim milk Other:…….....	2. Dairy products Chocolate, ice cream, whole milk Hard cheese, full-fat cheese – *Goat cheese, cheddar, Roquefort* – *Fontina, gruyere, parmesan, munster, and so on* Other:…….....
Laryngopharyngeal reflux treatment Drug: …….....	3. Cereals and starches Oat, wheat, cracker, pasta Wholemeal bread, brown bread Boiled potatoes, rice, brown rice Other:…….....	3. Cereals and Starches Chocolate cookies, peanut, white bread French fries and frying Nut, cashew, hazelnut Other:…….....
To take: before – during – after Meals (circle the adequate response) – Breakfast – Lunch – Dinner	4. Fruit and vegetables Agave, asparagus Banana, melon Broccoli, celery, fennel Cooked mushrooms Cauliflower, green beans, ginger Turnip, parsley, tofu Other:…….....	4. Fruit and vegetables Shallot Spicy Onion Chilli Tomato (sauce or raw tomato) Other:…….....
Drug: …….....	Preparation: Cooked by steaming or boiling in water	
To take: before – during – after Meals (circle the adequate response): –Breakfast –Lunch –Dinner	5. Beverage Chamomile Water, alkaline water Apple/pear juices (no sugar added) Melon/banana juices (no sugar added) Other:…….....	5. Beverage Strong alcohol, red and rosé wines Sparkling beverage (water, soda, beer, etc.) Coffee, tea Citrus juices (orange, grapefruit) Other:…….....
	6. Greasy substances Olive oil Other:…….....	6. Greasy substances Butter, spicy oils Sauces (mayonnaise, mustard, ketchup, etc.) Other:…….....
	7. Sugar Honey	7. Sugar Sweets

Diet and lifestyle modifications.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 22.0; IBM Corp., NY, USA). Changes in RSI, RFS, and voice quality assessments were analyzed with the Wilcoxon signed-rank test. The correlation study was conducted using Spearman's correlation test. A level of significance of 0.05 was adopted.

Results

Respectively 40 females and 40 males completed the study. From the 122 patients initially recruited, 42 were excluded for aerodigestive tract infections during the last month before the post-treatment consultation; absence to

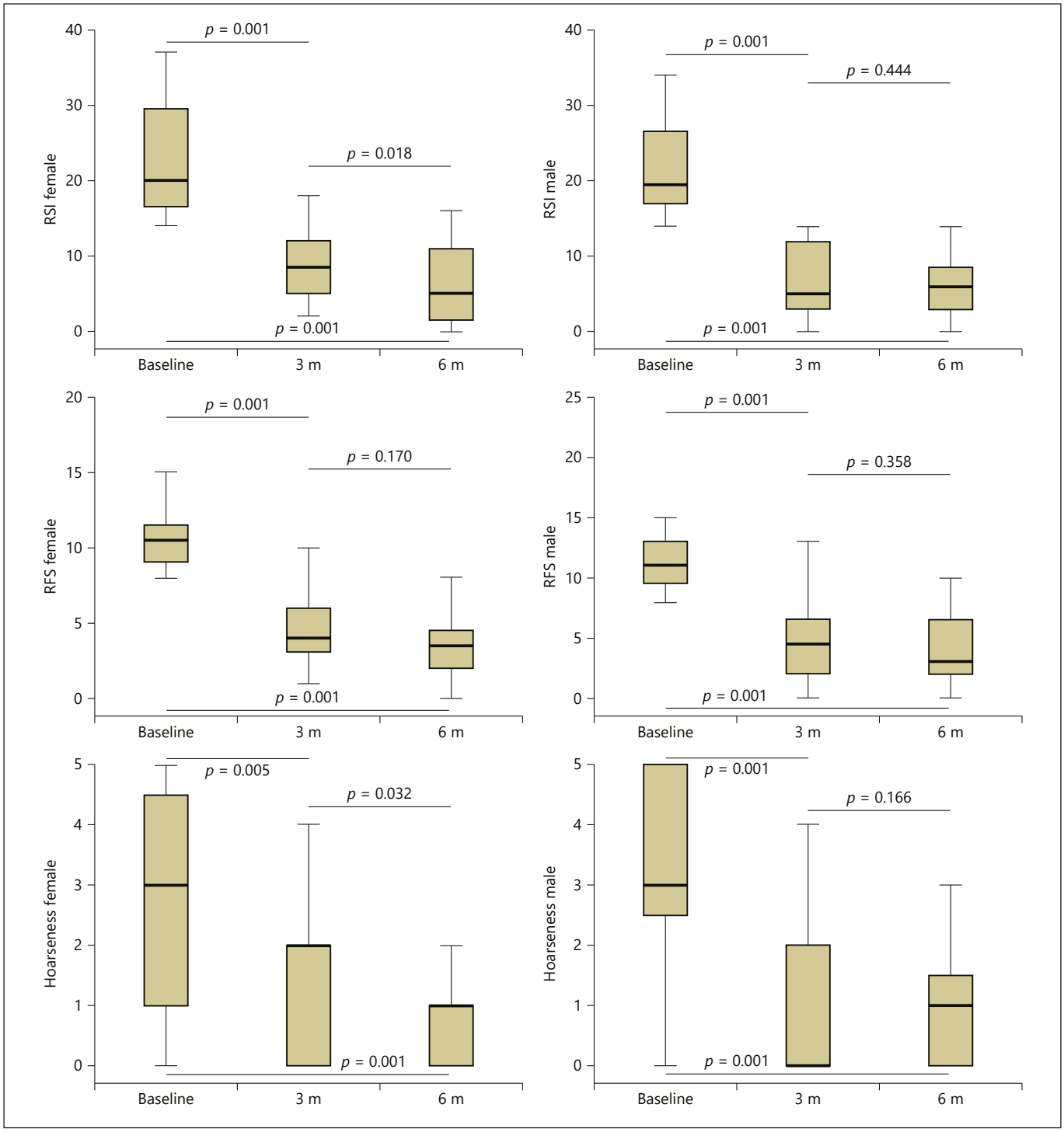


Fig. 1. Evolution of RSI, RFS, and hoarseness during the treatment period in male and female LPR patients. The statistical analysis was performed with Wilcoxon signed-rank test. RFS, reflux finding score; RSI, reflux symptom index.

the medical appointment 3 months after the treatment initiation; and stopping of treatment during the treatment period. Among the 80 patients who completed the study, 39 were cured after 3 months of treatment and 41 completed the 6-month follow-up (20 females and 21 males). The mean age of female and male was 47.6 and 55.0, respectively. Resistant patients had positive pH impedance metry.

Clinical and Voice Quality

The evolutions of RSI total score and items of both female and male groups are, respectively, described in Tables 2 and 3. The scores of RSI, hoarseness, troublesome cough, and globus sensation continued to improve from 3 to 6 months after the treatment initiation in female group. In male group, symptoms improved from baseline to 3 months post-treatment. We did not find significant improvement of symptoms from 3 to 6 months of treatment in male group. RFS score and the majority of individual RFS items significantly improved from baseline to 3 months of treatment in both groups and did not change from 3 to 6 months (Tables 2, 3). Evolutions of RSI, RFS, and the patient perception of hoarseness (RSI) according to gender are described in Figure 1. There was no statistical difference in the respect of diet and behavioral changes between groups ($p = 0.10$; Mann-Whitney test).

The evolution of acoustic measurements of males and females is described in Tables 2 and 3. After the first 3 months of treatment, we only found a significant improvement of acoustic parameters in male group. In female group, there was no change of acoustic measurements throughout the therapeutic period. The evolution of acoustic parameters according to gender is described in Figure 2.

The correlation study identified positive correlations between hoarseness, F0 (correlation coefficient: 0.313; $p = 0.049$), and Fhi (correlation coefficient: 0.350; $p = 0.027$) in male group. Besides this correlation, we did not find significant correlation between laryngoscopical findings and acoustic measurements in both groups.

Discussion

It was in 1960 that the association between reflux and laryngitis has been suspected for the first time [15]. Since then, many clinical studies established a clear relationship between LPR and the occurrence of voice disorders [16, 17]. On the one hand, it has been demonstrated that LPR patients had more voice quality disorders than healthy subjects [11, 12, 18]. On the other hand, many studies showed that voice quality improves throughout empirical therapeutic course, supporting the usefulness of voice quality assessment as therapeutic outcomes [1, 2, 19]. More recently, 2 case-control studies suggested that LPR females exhibited more voice quality impairments than LPR males [11, 12]. Nowadays, the potential gender-related differences about response to empirical treatment have not yet been studied. In this study, we identified that males and females have different clinical and voice quality patterns of change. Therefore, LPR males significantly improved the majority of symptoms, laryngoscopic findings, and acoustic parameters from baseline to 3 months of treatment, while the evolution of these assessments seems to be more complicated in LPR females. Indeed, females complained of hoarseness, cough, and globus longer than males. Moreover, although males significantly improved acoustic measurements throughout the 3 first months of treatment, females did not exhibit significant improvement of acoustic parameters along the therapeutic period.

Acoustic parameters are an interesting tool to identify subtle voice changes related to impairments of the vibratory process of the vocal folds. These measurements are particularly important in some laryngeal conditions characterized by mild or moderate dysphonia such as LPR [17, 20]. With regard to a recent review, percent shimmer and percent jitter would be the most interesting acoustic parameters as therapeutic outcomes [16, 17]. The acoustic improvement of male group and the lack of objectification of acoustic improvement in the female group could support a slower cure of LPR females compared to males. This gender-related susceptibility to LPR could be explained by anatomical, histological, and functional differences.

From an anatomical point of view, the vocal folds of females are characterized by shorter and thinner mucosa and smaller vibrating surface than those of males [21]. Thus, we hypothesized that the gastric or duodenal content's irritation of a thinner and shorter mucosa can lead to faster evaluable alterations of the smaller vibrating surface. In addition, it is possible that LPR induces more microscopic and macroscopic lesions of the vibratory margin of the vocal folds of females, which require more time to cure. Overall, these gender-related anatomical differences might partly explain the lower improvement of voice quality in female group. From a histological point of view, the superficial layer of the lamina propria of the female vocal folds is characterized by a smaller Reinke's space than that of males. According to some hypotheses supporting that LPR dysphonia is associated with dryness of Reinke's space [16], this gender-related histological characteristic could constitute an additional weakness factor for the development and the persistence of dysphonia related to reflux. Moreover, some authors recently suspected that the limited quantity of hyaluronic acid with additional dryness could

Table 2. Symptoms, signs, and acoustic evolution during treatment in LPR female group

Scales/parameters	Baseline	3 months	6 months	0–3 months	3–6 months
RSI	22.75±7.44	9.05±5.27	6.30±5.27	**<0.001**	**0.018**
Voice problem	2.70±1.83	1.54±1.37	0.80±0.11	**0.005**	**0.032**
Throat clearing	3.53±1.89	1.79±1.59	1.40±1.60	**<0.001**	0.390
Postnasal drip	2.68±2.02	1.15±1.41	0.85±1.09	**<0.001**	0.334
Dysphagia	1.45±1.58	0.59±1.12	0.25±0.64	**0.006**	0.063
Coughing posteating and lying down	2.15±2.07	0.49±1.00	0.50±1.24	**<0.001**	0.067
Choking and breathing difficulties	2.00±1.77	0.67±1.24	0.30±0.80	**<0.001**	0.066
Troublesome cough	2.55±1.93	0.69±0.92	0.25±0.55	**<0.001**	**0.016**
Globus pharyngeus	2.70±2.10	1.21±1.54	0.75±1.48	**<0.001**	**0.026**
Pyrosis, heartburn, and chest pain	3.00±1.84	1.03±1.31	1.15±1.27	**<0.001**	0.519
RFS	10.58±2.09	4.50±2.68	3.65±2.30	**<0.001**	0.170
Subglottic edema	0.05±0.32	0.01±0.01	0.01±0.01	0.317	1.000
Ventricular obliteration	1.20±1.56	0.41±0.94	0.20±0.62	**0.004**	0.157
Arytenoid/diffuse redness	2.75±1.08	1.49±1.00	1.20±1.01	**<0.001**	0.739
Vocal folds edema	1.33±0.80	0.33±0.53	0.35±0.67	**<0.001**	0.414
Diffuse laryngeal edema	1.35±0.98	0.46±0.68	0.15±0.37	**<0.001**	0.096
Posterior commissure hypertrophy	2.03±0.70	1.23±0.74	1.05±0.83	**<0.001**	0.059
Granuloma/granulation	0.63±0.93	0.21±0.62	0.30±0.73	**0.019**	0.317
Endolaryngeal mucous	1.30±0.97	0.46±0.85	0.50±0.89	**<0.001**	0.739
Objective voice quality					
Fundamental frequency					
F0	190.21±36.75	186.44±31.40	183.38±25.21	0.834	0.601
Fhi	217.29±44.33	209.20±32.60	205.20±32.19	0.252	0.687
Flo	167.63±37.76	166.97±34.14	165.69±24.65	0.696	0.445
F0 short-term perturbation cues					
Jitt	2.76±1.49	2.53±1.24	2.34±1.22	0.241	0.546
F0 mid-term perturbation cues					
PFR	5.61±2.99	5.13±2.64	4.81±2.39	0.586	0.520
STD	9.18±7.78	7.96±6.55	6.53±4.98	0.615	0.687
vF0	5.09±4.42	4.60±4.26	3.69±2.95	0.812	0.904
Intensity short-term perturbation cues					
Shim	6.56±3.01	6.44±2.73	6.05±2.92	0.759	0.717
Intensity mid-term perturbation cues					
vAm	15.67±5.54	14.78±4.64	13.85±3.35	0.357	0.494
Noise-related measurements					
NHR	0.18±0.06	0.18±0.05	0.90±3.20	0.696	0.687

The statistical analysis was performed with Wilcoxon signed-rank test. The figures in bold indicate significant *p* values.

RSI, reflux symptom index; dB, decibels; F0, fundamental frequency; Fhi, highest F0; Flo, lowest F0; Hz, Hertz; Jitt, percent jitter; LPR, laryngopharyngeal reflux; NHR, noise-to-harmonic ratio; PFR, phonatory fundamental frequency range; RFS, reflux finding score; s, second; Shim, percent shimmer; STD, standard deviation of F0; vAm, peak-to-peak amplitude variation; vF0, fundamental frequency variation.

lead to a decrease of the efficiency of the healing system, promoting vibratory trauma of phonation and epithelial alterations [22, 23]. Naturally, all of these explanations are hypotheses and need to be demonstrated in basic science studies.

From a functional perspective, males and females are known to have gender-related different vocal behaviors (i.e., posterior glottal gap, maximal glottal space, and opening pattern of the vocal folds) [24]. Overall, the posterior glottal gap, triangular glottal space, and posterior-

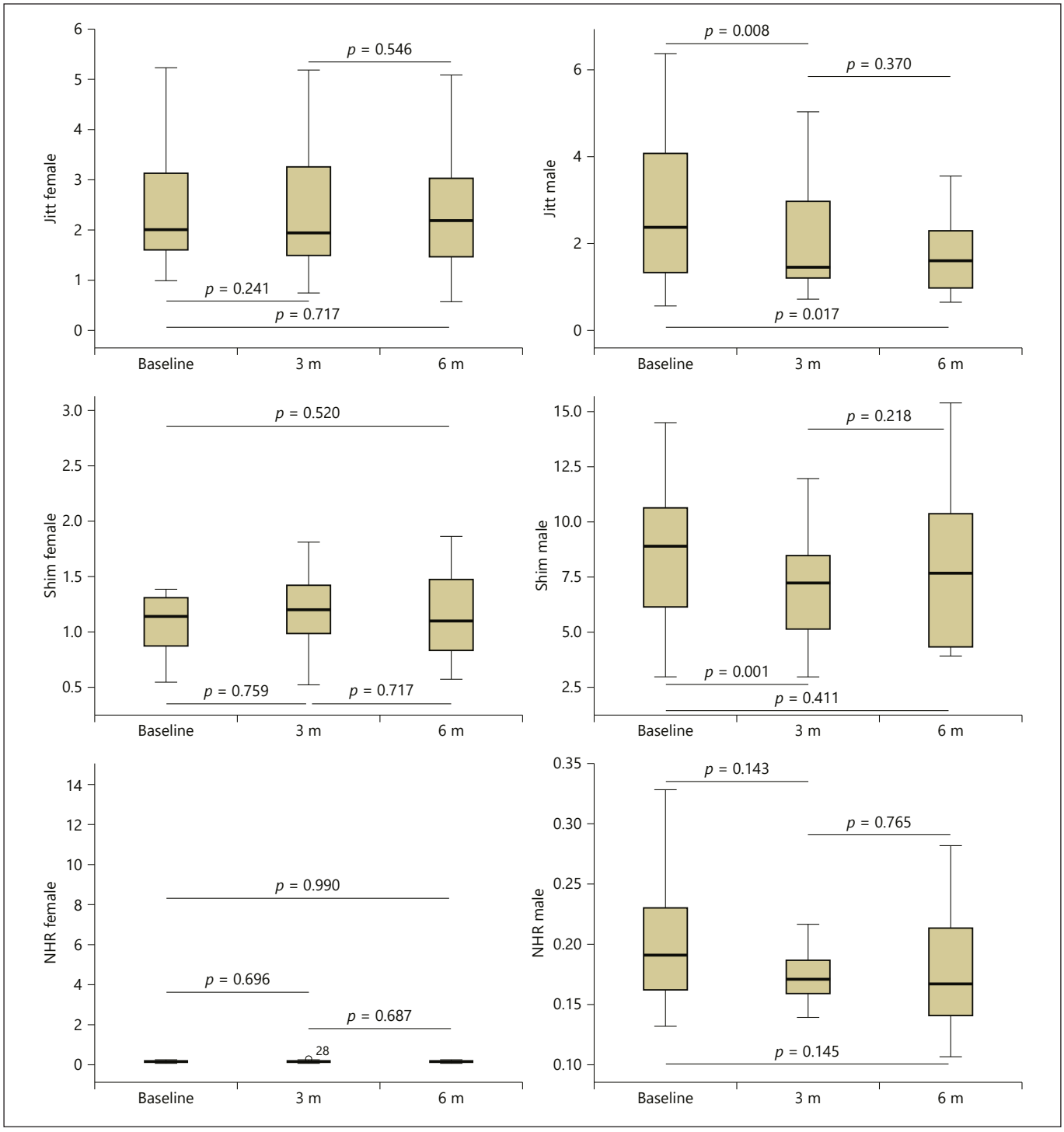
Table 3. Symptoms, signs, and acoustic evolution during treatment in LPR male group

Scales	Baseline	3 months	6 months	0–3 months	3–6 months
RSI	21.30±6.06	8.80±6.95	6.80±6.28	**<0.001**	0.444
Voice problem	2.73±1.60	1.05±1.15	1.05±1.05	**<0.001**	0.166
Throat clearing	3.73±1.54	1.78±1.39	1.60±1.39	**<0.001**	0.952
Postnasal drip	2.78±1.75	1.35±1.49	1.00±1.45	**<0.001**	0.371
Dysphagia	1.25±1.66	0.33±0.94	0.15±0.49	**0.002**	0.416
Coughing posteating and lying down	1.75±1.88	0.80±1.38	0.45±0.95	**0.006**	0.861
Choking and breathing difficulties	1.08±1.54	0.58±1.08	0.55±0.89	**0.032**	0.903
Troublesome cough	2.33±1.85	0.78±1.21	0.40±0.68	**<0.001**	0.748
Globus pharyngeus	2.60±1.77	0.93±1.39	0.55±1.05	**<0.001**	0.148
Pyrosis, heartburn, and chest pain	3.13±1.87	1.08±1.49	1.05±1.28	**<0.001**	0.904
RFS	10.73±2.66	5.25±3.58	3.80±3.02	**<0.001**	0.358
Subglottic edema	0.08±0.35	0.01±0.01	0.01±0.01	0.180	1.000
Ventricular obliteration	1.00±1.28	0.70±1.24	0.40±0.82	0.157	0.317
Arytenoid/diffuse redness	3.35±0.95	1.40±1.37	1.10±1.02	**<0.001**	0.305
Vocal folds edema	1.20±0.79	0.45±0.60	0.15±0.37	**<0.001**	0.058
Diffuse laryngeal edema	0.98±0.95	0.48±0.78	0.25±0.55	**0.008**	0.301
Posterior commissure hypertrophy	2.23±0.66	1.13±0.91	1.10±0.91	**<0.001**	0.248
Granuloma/granulation	0.50±0.88	0.35±0.77	0.30±0.73	0.257	0.564
Endolaryngeal mucous	1.35±0.95	0.65±0.95	0.50±0.88	**0.003**	1.000
Objective voice quality					
Fundamental frequency					
F0	123.57±24.09	125.41±27.98	123.17±22.41	0.619	0.881
Fhi	145.20±40.06	143.33±46.10	138.37±22.35	0.747	0.852
Flo	110.41±19.09	113.68±18.31	114.17±22.36	0.147	0.765
F0 short-term perturbation cues					
Jitt	2.49±1.51	2.25±2.88	1.79±0.99	**0.008**	0.370
F0 mid-term perturbation cues					
PFR	5.06±2.87	2.77±2.03	4.03±1.63	**0.006**	0.370
STD	5.89±6.91	5.48±11.17	3.54±1.81	0.053	0.247
vF0	4.00±3.38	3.52±4.33	2.78±1.51	**0.018**	0.263
Intensity short-term perturbation cues					
Shim	7.77±2.85	6.81±3.90	7.72±3.39	**0.001**	0.218
Intensity mid-term perturbation cues					
vAm	17.02±3.91	14.40±5.16	14.96±3.76	**<0.001**	0.765
Noise-related measurements					
NHR	0.19±0.05	0.19±0.12	0.18±0.05	0.143	0.765

The statistical analysis was performed with Wilcoxon signed-rank test. The figures in bold indicate significant *p* values.

RSI, reflux symptom index; dB, decibels; F0, fundamental frequency; Fhi, highest F0; Flo, lowest F0; Hz, Hertz; Jitt, percent jitter; LPR, laryngopharyngeal reflux; NHR, noise-to-harmonic ratio; PFR, phonatory fundamental frequency range; RFS, reflux finding score; s, second; Shim, percent shimmer; STD, standard deviation of F0; vAm, peak-to-peak amplitude variation; vF0, fundamental frequency variation.

to-anterior opening pattern of the vocal folds of females [24] are associated with the need to develop higher subglottic pressure threshold for the initiation of the vibration of the vocal folds [25]. The well-described LPR impairments of aerodynamic measurements (i.e., phonatory quotient and estimated subglottal pressure) [1, 26] could easily disrupt this glottal gap's proper balance, especially in LPR females who have more aerodynamic impairments than healthy females [17]. The long-time persistence of chronic inflammation of the mucosa re-



Color version available online

Fig. 2. Evolution of acoustic measurements during the treatment period in male and female LPR patients. Statistical significances are expressed by *p* value according to the Wilcoxon rank test. The statistical analysis was performed with Wilcoxon signed-rank test. Jitt, percent jitter; LPR, laryngopharyngeal reflux; NHR, noise-to-harmonic ratio; PQ, phonatory quotient; RFS, reflux finding score; RSI, reflux symptom index; Shim, percent shimmer.

lated to LPR and the continuation of forcing and compensatory vocal behaviors could explain the lower improvement of acoustic measurements and hoarseness perception of females compared to males. This observation may corroborate our previous anatomical and histological explanations because a more weakened mucosa needs more time to cure. In the same way, these hypotheses need to be confirmed with basic science and clinical studies.

With regard to our last hypothesis about functional gender-related differences, the first main weakness of this study is the lack of systematic evaluation of the stroboscopic vibratory characteristics of the vocal folds. The utilization of a standardized protocol to assess the vibratory process of the vocal folds would strengthen the current knowledge about the pathophysiological mechanisms underlying the development of hoarseness in LPR males and females. The second main weakness of this study concerns the lack of assessment of both subjective voice quality (i.e., perceptual voice assessment and voice handicap index) and aerodynamic measurements (mean estimated subglottal pressure, phonatory quotient), which may have strengthened our hypotheses. Indeed, the design and the pattern of evaluations of this preliminary study cannot confirm the suggested hypotheses. However, this study has brought to light the occurrence of gender-related differences in the therapeutic response of LPR disease. In the context of recent publications that strengthened the existence of gender differences in clinical presentation of LPR disease [11, 12, 26], further studies could explore the therapeutic response according to gender with a large panel of subjective and objective clinical and voice quality assessments. In the case of our observations are confirmed, the administration of different therapeutic schemes with, for example, various therapeutic durations regarding gender could be proposed.

The main weakness of this study is the lack of confirmed LPR diagnostic in patients because we did not systematically use pH impedance monitoring at baseline. In order to decrease the risk of inclusion of patients without LPR, we used the validated empirical approach of Belafsky et al. [9, 10], consisting of the use of RSI >13, RFS >7, and the careful exclusion of many differential diagnoses at baseline. Patients who did not respond to treatment benefited from additional examination, including pH impedance monitoring to confirm the diagnostic. This approach is not perfect but reduces the risk of inclusion of patients with laryngopharyngeal complaints not related to LPR in comparison with usual clinical diagnostic approach.

To date, no study really investigated the pattern of vibratory process of vocal folds of LPR patients considering gender differences. Future studies should also consider the study of vibratory process of the vocal folds of LPR patients according to gender. The use of videolaryngostroboscopy or high-speed camera will be required to better understand the gender-related differences supported in this study.

Conclusion

This preliminary study suggests the occurrence of gender-related differences in the LPR therapeutic response. Further studies need to clarify whether females require a longer course of therapy than males.

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Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors declare no conflicts of interest.

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