Impact of Laryngopharyngeal Reflux on Subjective, Aerodynamic, and Acoustic Voice Assessments of Responder and Nonresponder Patients

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Summary: Objective. To investigate the usefulness of voice quality assessment as a treatment outcome in responder and nonresponder patients with laryngopharyngeal reflux (LPR).

Material and methods. Eighty clinically diagnosed LPR patients with reflux finding score (RFS) > 7 and reflux symptom index (RSI) > 13 were treated with pantoprazole, lifestyle changes, and diet recommendations for three months. RSI; RFS; Voice Handicap Index; blinded Grade, Roughness, Breathiness, Asthenia, Strain, and Instability; aerodynamic and acoustic measurements were assessed at baseline and after treatment. These data were analyzed and compared with regard to the clinical evolution of patients (responder versus nonresponder). Patients who significantly improved RSI ≤ 13 and RFS ≤ 7 after treatment were considered as responder. Nonresponders were defined as patients with RSI > 13 and/or RFS > 7 at the end of treatment. Studies of correlation between the adherence to the diet regimen and the evolution of both signs and symptoms and between videolaryngostroboscopic signs; blinded Grade, Roughness, Breathiness, Asthenia, Strain, and Instability; and acoustic measurements were conducted.

Results. Significant improvements in RSI, RFS, Voice Handicap Index, perceptual voice quality (dysphonia and roughness), and some fundamental frequency and intensity perturbation cues (phonatory fundamental frequency range, percent jitter, pitch perturbation quotient, relative average perturbation, percent shimmer, smoothed amplitude perturbation quotient, amplitude perturbation quotient, and peak-to-peak amplitude variation) were mainly identified after treatment in responder patients. The clinical and voice quality improvements of nonresponder patients were lower; highlighting a similar evolution of symptoms, signs, and voice quality. The correlation analysis revealed significant relationships between the adherence to lifestyle changes and diet recommendations and the improvement of symptoms and substantial correlations between breathiness and fundamental frequency perturbation parameters.

Conclusion. Voice quality assessments can be used as indicators of the treatment effectiveness in patients with LPR. Voice quality improvement seems to be consistently associated with clinical improvement.

Key Words: Laryngopharyngeal–Reflux–Laryngitis–Acoustic–Quality of life–Voice.

INTRODUCTION

Laryngopharyngeal reflux disease (LPRD) is an inflammatory condition defined as the back flow of gastric contents into the laryngopharynx where it comes in contact with the tissues of the upper aerodigestive tract.[1] LPRD concerns 4%–30% of subjects who visit Otolaryngology Departments,[2,3] and up to 75% of patients with refractory ear, nose, and throat symptoms.[4] Hoarseness is a common symptom found in 71%–79% of patients[5,6] and may typically affect patient's quality of life via the development of a vocal handicap.[7] For two decades, many authors studied voice impairments in LPRD patients, particularly the use of voice quality assessments as outcomes.[3,8–10] Some authors showed acoustic improvement from baseline to 2, or 3 months posttreatment[3,8,9] while other did not find objective voice quality improvement along the treatment.[10–12] Several hypotheses can explain these controversial results. First, an important heterogeneity characterized these studies about the diagnosis of LPRD, and the related inclusion of patients, which may bias the comparability between studies. Indeed, LPRD diagnosis is a subject of controversy, particularly the systematic use of pH-impedance metry since some evidences (ie, high false-positive and false-negative rates, interpretation difficulties, inconsistency between pH findings, signs, and symptoms) suggested that this method is not perfect.[13,14] Second, the methodological discrepancies between studies concerning objective voice quality

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assessment, especially acoustic measurements, make the comparison difficult.[9] Moreover, to date, none of these trials have studied voice quality impairments with a complete assessment including at least subjective, aerodynamic, and acoustic measurements. This point is particularly relevant because it still important to use a large panel of evaluations of voice quality (including self and perceptual assessments, aerodynamic, and acoustic measurements) for the study of voice quality as therapeutic outcome and for the identification of the best outcomes. Another question that remains unanswered concerns the voice quality evolution of patients who clinically did not respond to treatment. No study interested to the evolution of voice quality of this group of patients and we do not know if voice quality similarly evolves than signs and symptoms related to laryngopharyngeal reflux (LPR).

The objectives of this study are to investigate the usefulness of voice quality as therapeutic outcome in responder and nonresponder LPRD patients and to compare voice quality evolution with clinical and quality of life evolutions along the treatment.

MATERIALS AND METHODS

Ethical considerations

This study has been approved by the local ethics committee (ref. 2015/99-B707201524621).

Subject characteristics

From September 2013 to April 2016, we prospectively recruited 122 outpatients with LPRD-related symptoms at the Otolaryngology Departments of both EpiCURA Hospitals and Liege University Hospital. The suspicion of the LPRD diagnosis was based on the utilization of both scales reflux symptom index (RSI $>$ 13) and reflux finding score (RFS $>$ 7); these two thresholds being significantly correlated with a positive double-probe pH monitoring result and the LPRD diagnosis.[15,16] To reduce the risk to include patients with cofactors able to bias the study, we excluded patients with the following criteria: vocal overuse, neurological disease affecting voice, psychiatric illness, upper respiratory tract infections within the last month, an antacid treatment already started (ie, proton pump inhibitor[s] [PPI {s}], gastroprokinetic, or antihistamine), previous history of cervical surgery or radiotherapy, laryngeal trauma, vocal cord paralysis/paresis, benign vocal fold lesions, pharyngolaryngeal malignancy, seasonal allergies, asthma, chronic obstructive pulmonary disease, PPI hypersensitivity, untreated thyroid disease, prior antireflux surgery, or chemical exposure causing laryngitis. Moreover, active smokers, alcoholics, and pregnant and lactating women were also excluded.

From these 122 patients, 80 completed the study and 42 were excluded for many reasons, that is aerodigestive tract infections during the last month before the posttreatment consultation, the absence to the medical appointment 3 months after the treatment initiation, the stopping of treatment during the treatment period, etc. The characteristics (ie, age, gender, body mass index, and adverse reactions) and the main complaints of patients were available in Table 1. From the selected patients with RSI $>$ 13 and RFS $>$ 7 at baseline, we studied two groups according to treatment response after 3 or, in the case of a 3-month uncompleted improvement, 6 months of treatment.

Precisely, with regard to the initial publications of Belafsky et al, patients with a significant reduction of both RSI $\leq$ 13 and RFS $\leq$ 7 (below the critical thresholds) after treatment were defined as responder patients.[15,16] This first group included 59 patients. Patients who did not improve RSI, RFS, or both below the thresholds were considered as nonresponder patients. This second group included 21 patients. Because the LPRD diagnosis could remain suspect in these patients, they benefited from additional examination (ie, pH-impedance metry, esogastroduodenoscopy, etc) to confirm the diagnosis. Overall, to improve patient care,[13] we used a clinically validated protocol[17] for the management of LPRD patients (Figure 1).

Patients were treated by diet, lifestyle changes, and twice-daily proton pump inhibitors (PPIs, 20 mg pantoprazole). Lifestyle changes included reduction of tobacco, alcohol consumption, smaller meals, and early diners. Concerning the diet regimen, each patient received personalized recommendations in the form of a French recommendation grid based on both diet habits of our country and the Koufman's work (Table 2).[17] The adherence of the recommendations of this grid was accurately assessed by the patient and the physician after the treatment period using a point-scale with results between 0 (nonadherent) and 10 (fully adherent to the recommendations).

Clinical evaluations, subjective voice assessments, and quality of life

Patients were clinically assessed at baseline and after 3 months of treatment with RSI and RFS. To identify the patient's status (responder or nonresponder), nonresponder subjects were clinically reevaluated at 6 months with both RSI and RFS. The only aim of the second evaluation of the nonresponders at the 6 months was to identify those who needed additional examinations and treatment. RFS was evaluated using videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany). In practice, at baseline and at the end of treatment, patients received instructions to fulfill RSI, Voice Handicap Index (VHI) and the Short Form 36 Health Survey before the consultation (in waiting room), and they were seen by the first author of this study (JRL) for the study's inclusion, the voice quality evaluations, and the treatment explanations. A second experienced laryngologist (MK) made the RFS evaluations in a blind manner in regard to the patient complaints (RSI). Moreover, the presence of enlarged lingual tonsils, which was described as an additional LPRD sign,[19]

TABLE 1.
Clinical Characteristics of Patients

	Clin. diag. LPR patients		Responder LPR patients		Nonresponder patients	
	Total (80)	%	Total (59)	%	Total (21)	%
Mean age (years)	51.3	-	51.90	-	48.93	-
BMI (kg/m^2)	26.36	-	26.12	-	27.42	-
Gender (M/F)	40/40	50/50	28/31	47/53	12/9	57/43
Adverse reactions	0	0	0	0	0	0
Main complaints						
Globus sensation	16	20%	12	20%	4	20%
Dysphonia	16	20%	10	17%	6	30%
Cough	11	13.75%	9	16%	2	10%
Odynophagia	9	11.25%	7	12%	2	10%
Heartburn	7	8.75%	6	10%	1	4%
Throat clearing	6	7.5%	5	7%	1	4%
Dysphagia	5	6.25%	3	5%	2	10%
Sticky expectorations/Xerostomia	4	5.00%	2	3%	1	4%
Postnasal drip	3	3.75%	3	5%	1	4%
Otalgia	1	1.25%	1	2%		
Dyspepsia	1	1.25%			1	4%
Breathing difficulties	1	1.25%	1	2%		
All complaints						
Throat clearing	76	95%	55	93%	21	100%
Dysphonia	68	85%	51	86%	17	81%
Heartburn	69	86%	50	85%	19	90%
Postnasal drip/Sticky expectorations	63	79%	48	81%	15	71%
Cough	62	78%	47	80%	15	71%
Globus sensation	61	76%	46	78%	15	71%
Cough after eating/lying down	47	59%	36	61%	11	52%
Breathing difficulties	46	58%	34	58%	12	57%
Dysphagia	41	51%	30	51%	11	52%
Tongue tonsil hyp.	18	22.5%	12	20,30%	6	28.6%

The entire cohort was composed of 80 LPRD subjects divided in two groups: responder and nonresponder patients. There is no statistically difference between groups concerning mean age, gender, and BMI (respectively $P = 0.628$, $P = 0.449$, and $P = 0.938$; Mann-Whitney U test).
Abbreviations: BMI, body mass index; Hyp, hypertrophy.

was also assessed at the first consultation (mild/moderate/severe). To study potential differences in the individual evolution of symptoms and signs, we interested to the improvement of each item of the two questionnaires.

The perceptual voice evaluation (Grade, Roughness, Breathiness, Asthenia, Strain, and Instability [GRBASI scale]) of hoarse patients was performed by a jury of experienced listeners (three inter-reliable[20] experienced speech therapists) who were blinded concerning the time of the recording. They used connected speech to grade the GRBASI scores (0−3). Patient management is described in Figure 1.

Aerodynamic and acoustic measurements

Maximum phonation time (MPT), phonatory quotient (PQ), slow vital capacity (VC, to calculate PQ), and S/Z ratio were measured using a calibrated spirometer that takes into account age, sex, height, and ethnicity of the patient (Spiro-USB100; Medical Electronic Construction, Brussels, Belgium). MPT was tested three times with sustained /a/ and only the best value was considered for the study. PQ was defined as the ratio between VC (mL) and MPT (seconds).

To measure acoustic parameters, subjects were asked to produce three times the /a/ vowel, holding the utterance as long as possible. In this study, first, we measured MPT and, second, we measured acoustic parameters. The measurement of the acoustic cues was made on the entire signal of the three vowels (excluding the first and the last usual instable milliseconds of the signal). Voice recordings were performed by the same practitioner (JRL) during the consultation in a sound-treated room with a high-quality microphone (Sony PCM-D50; NY, USA) placed at a distance of 30 cm from the patient's mouth.[19] The acoustic parameters were measured using MDVP software (KayPentax, NJ, USA) and included Fundamental frequency (F0, with regard to gender), Standard Deviation of F0 (STD), Fundamental frequency variation (vF0), Jitter percent (Jitt), Relative Average Perturbation (RAP), Pitch Perturbation Quotient (PPQ), Smoothed Pitch Perturbation Quotient, Phonatory Fundamental Frequency Range (PFR),

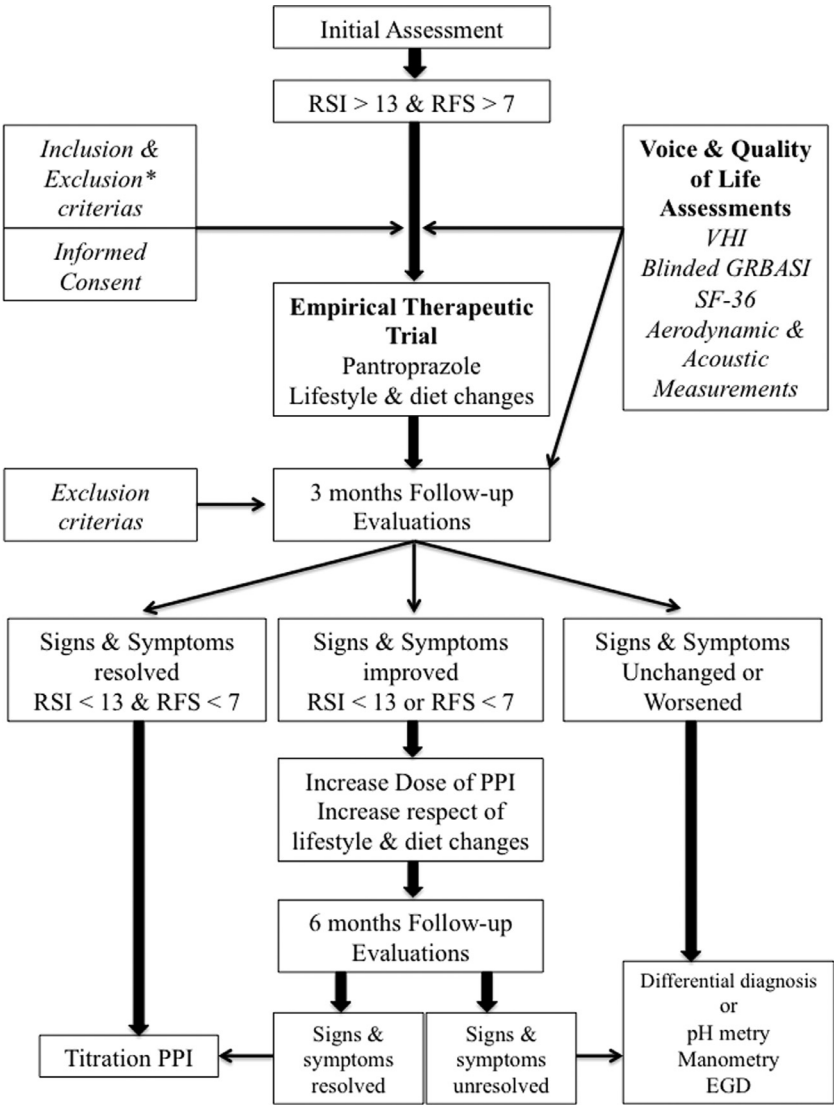

FIGURE 1. Flow chart describing the algorithm for assessment and management of patients.
Patients with LPRD symptoms (RSI > 13) and signs (RFS > 7) were recruited and assessed at baseline and treated by PPIs and diet advices during 3 months. A second clinical and voice quality assessment was made after 3 months. The treatment of the responder patients (RSI ≤ 13 and RFS ≤ 7) was titrated and the therapy of nonresponder patients was adapted (maintained of increased PPIs doses). Physician provided a third clinical evaluation at 6 months for nonresponder patients. Additional examinations (ie, esogastroduodenoscopy and pH metry and manometry) were recommended for these patients.

Shimmer percent (Shim), Amplitude Perturbation Quotient (APQ), Smoothed Amplitude Perturbation Quotient (sAPQ), Peak-to-Peak Amplitude Variation (vAm), Noise Harmonic Ratio, Voice Turbulence Index, and Soft Phonation Index.

To better understand the relationships between subjective and objective observations, we conducted a correlation study between clinical characteristics, components of RSI, RFS, adherence to diet and behavioral changes, perceptual voice assessments, and aerodynamic and acoustic measurements.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS v22.0; IBM Corp., NY, USA). According to an initial analysis of the data distribution (non-Gaussian), the following statistical nonparametric tests were used: Wilcoxon signed-rank test (precomparisons/postcomparisons), Mann-Whitney test (comparison between groups), and Spearman correlation test (correlations). A level of significance of 0.05 was adopted.

RESULTS

Clinical evolution

The values of the RSI and RFS total and item scores significantly decreased from baseline to posttreatment in the responder group at the exception of granulation and subglottic edema scores (Table 3). In nonresponder group, total RSI and RFS scores significantly improved after treatment

TABLE 2.
French Diet, Behavioral and Lifestyle Changes Grid

Habitudes de vie	Alimentation à privilégier	Alimentation à éviter
1. Réduire son stress	1. Viandes, poissons, volailles et oeufs	1. Viandes, poissons, volailles et oeufs
2. Réduire sa consommation de:	Poissons frais maigres	Poissons gras
-Tabac	Crevettes, homard et mollusques	Huiles de poissons (sardines, morue, hareng)
-Autre	Poulet (blanc, sans peau)	Volaille grasse
3. Réduire la taille de ses repas	Dinde (blanc, sans peau)	Viandes riches en graisses*
4. Privilégié les repas chauds à midi	Canard	*-Rognons*
5. Manger lentement	Viandes pauvres en graisses**	*-Lards*
6. Eviter de parler en mangeant	*-Escalope de veau*	*-Viandes à base de haché*
7. Eviter les vêtements trop serrés	*-Jambon blanc dégraissé*	*-Pâtés*
8. Eviter si possible, en accord avec les	*-Steak, faux-filet et filet*	*-Tripes*
confrères les médicaments favorisant*	*-Rôti de veau*	*-Mouton*
-Anti-inflammatoires non stéroïdiens	*-Filet mignon de porc*	*-Epaule, gigot, côtelettes d'agneau*
-Corticoïdes, aspirine, théophylline	*-Cheval*	*-Côte, entrecôtes de boeuf*
-Certains antibiotiques	*-Côte de veau*	*-Côtelettes, rôti, échine de porc*
-Progestérone, suppléments en Fer	**Retrait du gras souhaitable	*-Foie gras*
-Dérivés nitrés et inhibiteurs calciques	Blanc d'oeuf	*-Charcutries*
En cas de brûlant d'estomac en plus	2. Produits laitiers	2. Produits laitiers
1. Réduire le surpoids	Fromage maigre	Chocolat
2. Relever la tête du lit pour dormir	Lait écrémé	Crèmes glacées
		Fromages gras et à pâte dure
		-Fromages de chèvre, cheddar, roquefort,
		-Fontina, gruyère, parmesan, munster, etc
		Lait entier
Medicaments	3. Céréales et féculents	3. Céréales et féculents
Nom:	Avoine	Biscuits chocolatés
	Blé	Cacahuèttes
A prendre: Avant - Pendant - Après	Blé à semoule	Fritures et frittes
	Cracker	Noix, noix de cajou, noisettes
Les repas:	Molusque	Noix de macadamia
	Pain gris/complet	Pain blanc
-Petit déjeuner (ou déjeuner, Belgique)	Pâtes	
	Pomme de terre (cuites à l'eau)	
-Déjeuner (ou dîner, Belgique)	Riz, riz brun	
	4. Fruits et légumes	4. Fruits et légumes
-Diner (ou souper, Belgique)	Agave	Echalotes
	Asperge	Epices
Nom:	Banane	Oignons
	Brocolis	Piments
A prendre: Avant - Pendant - Après	Celeri	Tomates (crues et sauces)
	Champignons cuits	
Les repas:	Choux fleur	
	Fenouil	
-Petit déjeuner (ou déjeuner, Belgique)	Gingembre	
	Haricots verts	
-Déjeuner (ou dîner, Belgique)	Melon	
	Navet	
-Diner (ou souper, Belgique)	Persil	
	Tofu	
Nom:	5. Boissons	5. Boissons
	Camomille	Alcool forts
A prendre: Avant - Pendant - Après	Eau	Boissons pétillantes (eau, sodas, bières, etc)
	Jus de pomme/poire bio	Café et thé
Les repas:	Jus de melon	Jus à base d'agrumes: orange, citron, pamplemousse
	(sans sucre ajouté)	Vins rouges et rosés
-Petit déjeuner (ou déjeuner, Belgique)	6. Corps gras	6. Corps gras
	Huile d'olive	Beurre
-Déjeuner (ou dîner, Belgique)		Huiles pimentées et épicées
		Sauces
-Diner (ou souper, Belgique)	7. Sucres	7. Sucres
	Miel	Confiseries

Diet and lifestyle changes are described in this grid that is distributed to patient. The respect of the recommendations of this grid was assessed from 0 (=no respect) to 10 (=exclusion of all proreflux foods). This grid was partly based on the Koufman's work[18] and adapted according to the diet habits of our country.

TABLE 3.
Pretreatment and Posttreatment Clinical Assessments in Responder and Nonresponder LPRD Patients

Scales	Responder LPR patients				Nonresponder LPR patients*			
	Pretreatment	Posttreatment	*Z*	*P* value†	Pretreatment	Posttreatment	*Z*	*P* value†
RSI	22.42 ± 7.07	6.93 ± 4.75	−6.67	<0.001	20.90 ± 5.89	14.52 ± 6.19	−3.66	<0.001
Voice problem	2.81 ± 1.73	0.95 ± 1.10	−5.32	<0.001	2.43 ± 1.66	2.24 ± 1.30	−0.29	0.774
Throat clearing	3.54 ± 1.85	1.45 ± 1.40	−5.25	<0.001	3.86 ± 1.28	2.71 ± 1.31	−2.61	0.009
Postnasal drip	2.71 ± 1.86	0.95 ± 1.29	−4.95	<0.001	2.76 ± 1.97	2.10 ± 1.55	−1.81	0.070
Dysphagia	1.31 ± 1.58	0.41 ± .99	−3.54	<0.001	1.48 ± 1.75	0.57 ± 1.17	−2.11	0.035
Coughing posteating and lying down	2.15 ± 2.04	0.50 ± 1.05	−4.82	<0.001	1.38 ± 1.69	1.05 ± 1.53	−0.83	0.404
Breathing difficulties	1.49 ± 1.61	.38 ± .83	−4.32	<0.001	1.67 ± 2.01	1.29 ± 1.62	−0.87	0.382
Troublesome cough	2.56 ± 1.95	0.50 ± 0.84	−5.53	<0.001	2.10 ± 1.67	1.38 ± 1.36	−1.94	0.053
Globus pharyngeus	2.68 ± 1.94	0.93 ± 1.34	−5.17	<0.001	2.57 ± 1.94	1.43 ± 1.75	−2.89	0.004
Pyrosis, heartburn, and chest pain	3.05 ± 1.94	0.78 ± 1.11	−5.81	<0.001	3.10 ± 1.58	1.81 ± 1.81	−3.05	0.004
RFS	10.41 ± 1.93	4.08 ± 2.52	−6.63	<0.001	11.33 ± 3.29	7.10 ± 3.75	−3.82	<0.001
Subglottic edema	0.07 ± 0.37	0.01 ± 0.01	−1.41	0.157	0.05 ± 0.22	0.00 ± 0.00	−1.00	0.317
Ventricular obliteration	1.05 ± 1.41	0.28 ± 0.79	−3.63	<0.001	1.24 ± 1.48	1.33 ± 1.46	−0.33	0.739
Arytenoid/diffuse redness	3.02 ± 1.08	1.38 ± 1.14	−5.37	<0.001	3.14 ± 1.01	1.62 ± 1.36	−2.96	0.003
Vocal folds edema	1.34 ± 0.78	0.38 ± 0.52	−5.33	<0.001	1.05 ± 0.81	0.43 ± 0.68	−2.70	0.007
Diffuse laryngeal edema	1.17 ± 0.99	0.31 ± 0.60	−4.37	<0.001	1.14 ± 0.96	0.95 ± .89	−1.39	0.166
Posterior commissure hypertrophy	2.10 ± 0.66	1.10 ± 0.74	−5.64	<0.001	2.19 ± 0.75	1.38 ± 1.02	−3.02	0.003
Granuloma/granulation	0.39 ± 0.79	0.24 ± 0.66	−1.19	0.233	1.05 ± 1.02	0.38 ± .81	−2.65	0.008
Endolaryngeal mucous	1.29 ± 0.97	0.45 ± 0.84	−4.23	<0.001	1.43 ± 0.93	0.86 ± 1.01	−2.12	0.034

* Among the nonresponder patients, we did not report significant differences between patients who exclusively exhibited improved RSI compared with those exhibiting exclusive enhancement in RFS.
† Wilcoxon signed-rank test.
Abbreviation: Z, statistic difference.

TABLE 4.
Pretreatment and Posttreatment Subjective Voice Quality and Quality of Life Assessments in Responder and Nonresponder LPRD Patients

Scales	Responder LPR patients				Nonresponder LPR patients			
	Pretreatment	Posttreatment	*Z*	*P* value	Pretreatment	Posttreatment	*Z*	*P* value
VHI	17.58 ± 14.19	10.17 ± 10.16	−4.60	<0.001	20.47 ± 16.06	10.89 ± 9.64	−2.88	0.004
VHIe	3.57 ± 4.63	2.12 ± 3.46	−3.79	<0.001	4.21 ± 5.31	2.21 ± 3.39	−1.17	0.244
VHIp	9.56 ± 6.66	5.38 ± 5.09	−4.80	<0.001	10.95 ± 8.86	6.37 ± 5.67	−2.47	0.014
VHIf	4.35 ± 5.17	2.67 ± 3.24	−2.88	0.004	5.26 ± 4.01	2.32 ± 2.27	−2.78	0.005
Grade	0.96 ± 0.81	0.52 ± 0.58	−2.18	0.029	1.08 ± 0.67	0.83 ± 0.72	−1.13	0.257
Roughness	0.89 ± 0.64	0.56 ± 0.51	−2.18	0.029	1.00 ± 0.74	0.75 ± 0.62	−1.34	0.180
Breathing	0.30 ± 0.54	0.30 ± 0.54	−.00	1.00	0.50 ± 0.67	0.50 ± 0.80	−.00	1.00
Asthenia	0.15 ± 0.36	0.26 ± 0.48	−1.34	0.180	0.42 ± 0.67	0.58 ± 0.79	−1.00	0.317
Strain	0.70 ± 0.67	0.41 ± 0.57	−1.89	0.059	1.00 ± 1.04	0.75 ± 0.75	−0.97	0.334
Instability	0.70 ± 0.78	0.37 ± 0.49	−1.90	0.058	0.75 ± 0.62	0.58 ± 0.67	−0.58	0.564
SF-36								
Physical functioning	81.30 ± 19.74	85.56 ± 17.31	−3.05	0.002	81.43 ± 17.59	85.00 ± 22.36	−0.76	0.448
Role-physical	63.43 ± 36.89	74.07 ± 32.93	−2.41	0.016	60.71 ± 41.27	80.36 ± 31.28	−1.56	0.119
Bodily pain	67.67 ± 29.72	79.50 ± 24.94	−2.95	0.003	75.14 ± 29.39	79.50 ± 27.51	−0.63	0.527
General health	59.70 ± 16.93	66.19 ± 16.11	−3.12	0.002	55.29 ± 20.59	64.36 ± 19.19	−1.92	0.055
Vitality	51.98 ± 19.36	63.65 ± 19.73	−4.11	<0.001	55.29 ± 24.40	58.50 ± 19.80	−0.84	0.400
Social functioning	74.39 ± 24.62	87.30 ± 16.30	−3.65	<0.001	76.00 ± 34.49	81.43 ± 21.11	−0.49	0.623
Role-emotional	72.15 ± 39.31	87.02 ± 29.31	−3.07	0.002	64.29 ± 42.34	80.86 ± 31.41	−2.33	0.020
Mental health	61.85 ± 21.23	71.54 ± 17.79	−4.43	<0.001	57.00 ± 20.77	62.07 ± 19.72	−1.33	0.183
Physical health	68.02 ± 20.90	76.33 ± 17.41	−3.84	<0.001	68.14 ± 19.33	77.30 ± 19.56	−2.06	0.039
Mental health	65.09 ± 20.72	77.38 ± 17.06	−5.40	<0.001	63.14 ± 25.47	70.71 ± 17.71	−1.54	0.124

Wilcoxon signed-rank test.
Abbreviations: SF-36, short form health survey; VHI e/p/f, voice handicap index emotional, physical, functional; *Z,* statistic difference.

but the improvement of item scores was more disparate compared to the responder group (Table 3).

According to Mann-Whitney test, nonresponder patients had significant higher scores of dysphonia ($P < 0.001$), throat clearing ($P = 0.001$), breathing disorders ($P = 0.004$), and cough ($P = 0.002$) than responder patients at the post-treatment time.

Concerning the videolaryngostroboscopic observations, at baseline, nonresponder patients had higher scores of diffuse laryngeal edema ($P = 0.001$), and granulation ($P = 0.001$; Mann-Whitney test) than responder subjects. Nonresponder subjects also presented more important tongue tonsil hypertrophy than responder patients (12.1% versus 27.3% of cases) in a context of similar rate of obstructive sleep apnea (OSA, 8.6% in responder versus 13.6% in nonresponder patients).

The mean scores of respect of diet and lifestyle changes were respectively 6.72 ± 0.21 and 5.66 ± 0.45 in responder and nonresponder patients. Our analysis showed that responder patients had respected lifestyle changes and diet regimen better than nonresponder subjects ($P = 0.041$, Mann-Whitney test).

The study of correlations reported positive relationships between the pyrosis sensation and the presence of endolaryngeal mucus ($P = 0.044$) and negative correlations between the patient's age and the pyrosis sensation ($P = 0.003$) and between body mass index and endolaryngeal mucus score ($P < 0.001$). Significant correlations between the adherence to the diet regimen and the enhancement of RSI total score ($P < 0.001$), throat clearing ($P = 0.006$), cough ($P = 0.005$), globus ($P = 0.010$), and pyrosis ($P = 0.008$) were identified. We did not identify significant correlation between the improvement of RFS items and the respect of diet and behavioral changes.

Subjective voice quality

The scorings of VHI components significantly decreased after treatment in both groups (Table 4). From the blinded perceptual evaluations of the three judges, significant improvements of mean grade of dysphonia and roughness were only reported in responder group. In the nonresponder group, we did not find significant improvement of perceptual voice quality.

TABLE 5.
Correlation Study (*P* Values) Between SF-36 and VHI Scores

SF-36 scores	LPR patients			
	VHItot	VHIf	VHIe	VHIp
Physical functioning	0.116	−0.040	0.131	0.285
Role-physical	−0.044	−0.008	−0.012	0.381
Bodily pain	−0.012	−0.007	0.136	−0.02
General health	0.269	0.115	0.417	0.324
Vitality	0.163	0.467	0.117	0.166
Social functioning	−0.012	0.015	−0.019	0.055
Role-emotional	0.427	0.419	0.317	0.695
Mental health	0.432	0.727	0.127	0.545
Physical health	−0.018	−0.002	−0.020	0.124
Mental health	0.087	0.123	−0.045	0.201

The *P* values available in this table were calculated using Pearson correlation test.
Abbreviations: SF-36, short form health survey; VHI e/p/f, voice handicap index emotional, physical, functional.

Quality of life assessment

The enhancement of quality of life was better in nonresponder group than responder group (Table 4). Significant correlations were identified between the physical health score of SF-36 and VHItot, VHIf, VHIe and between mental health score and VHIe (Table 5).

Aerodynamic and acoustic measures

We did not find significant improvement of MPT and PQ in both responder and nonresponder groups along the treatment. However, MPT tended to improve after treatment in responder patients (Table 6).

The most obvious acoustic improvements after treatment concerned the intensity and frequency short-term perturbation parameters, which were only found in responder group. They included Jitt, RAP, PPQ, vAm, Shim, APQ, and sAPQ (Table 7). F0 did not improve along the treatment in both male and female irrespective to the group. We did not identify acoustic improvement in nonresponder subjects. Significant correlations between the mean scores of breathiness and the values of Jitt, RAP, PPQ, PFR, STD, and vF0 of the assessed samples were identified (Table 8).

TABLE 6.
Aerodynamic Measurements in Responder and Nonresponder LPRD Patients

Aerodynamic measurements	Units	Responder LPR patients				Nonresponder LPR patients			
		Pretreatment	Posttreatment	*Z*	*P* value	Pretreatment	Posttreatment	*Z*	*P* value
MPT	s	15.06 ± 6.74	16.14 ± 6.28	−1.45	0.147	14.88 ± 9.90	17.55 ± 10.43	−1.89	0.058
PQ	mL/s	271.45 ± 105.50	249.41 ± 80.97	−1.65	0.099	287.62 ± 173.47	253.52 ± 135.63	−1.34	0.179
S/Z	-	1.06 ± 0.57	1.06 ± 0.54	−.16	0.873	1.01 ± 0.20	0.97 ± 0.33	−0.71	0.477

Wilcoxon signed-rank test.
Abbreviations: mL/s, milliliter/second; s, second; *Z*, statistic difference.

TABLE 7.
Pretreatment and Posttreatment Acoustic Measurements in Responder and Nonresponder LPRD Patients

Acoustic parameters	Units	Pretreatment	Posttreatment	*Z*	*P* value	Pretreatment	Posttreatment	*Z*	*P* value
F0 short-term perturbation cues									
Jitt	%	2.65 ± 1.50	2.21 ± 1.20	−2.30	0.022	2.57 ± 1.53	2.88 ± 3.83	−1.58	.114
RAP	%	1.58 ± 0.89	1.32 ± 0.72	−2.28	0.023	1.52 ± 0.90	1.69 ± 2.22	−1.58	.114
PPQ	%	1.60 ± 0.94	1.34 ± 0.78	−2.20	0.028	1.57 ± 0.99	1.81 ± 2.66	−1.79	.073
sPPQ	%	2.45 ± 1.99	2.05 ± 1.45	−1.28	.220	2.45 ± 1.73	3.01 ± 4.32	−1.13	.259
F0 mid-term perturbation cues									
PFR		5.28 ± 2.94	4.49 ± 2.14	−1.75	0.079	5.46 ± 2.92	5.31 ± 3.92	−1.03	0.305
STD	Hz	7.32 ± 7.36	5.69 ± 4.80	−1.38	0.167	8.05 ± 7.99	9.51 ± 15.94	−0.82	0.414
vF0	%	4.35 ± 3.74	3.61 ± 2.97	−1.28	0.200	5.06 ± 4.50	5.27 ± 6.70	−0.85	0.394
Intensity short-term perturbation cues									
Shim	%	6.97 ± 3.10	6.16 ± 2.47	−2.39	0.017	7.73 ± 2.60	7.92 ± 4.92	−0.92	0.357
APQ	%	4.46 ± 2.31	4.87 ± 1.94	−2.09	0.037	6.17 ± 2.01	6.25 ± 3.91	−1.16	0.244
sAPQ	%	9.58 ± 3.22	8.50 ± 2.84	−2.33	0.020	10.27 ± 2.86	9.45 ± 2.97	−1.37	0.170
Intensity mid-term perturbation cues									
vAm	%	16.07 ± 4.62	14.19 ± 4.49	−2.76	0.006	17.14 ± 5.31	15.70 ± 5.82	−1.83	0.068
Noise-related measurements									
NHR		0.18 ± 0.06	0.17 ± 0.04	−0.87	0.384	0.19 ± 0.06	0.21 ± 0.16	−0.87	0.375
VTI		0.06 ± 0.06	0.07 ± 0.13	−0.50	0.618	0.07 ± 0.05	0.06 ± 0.03	−0.64	0.520
SPI		18.59 ± 7.96	17.34 ± 8.01	−1.46	0.144	15.62 ± 6.15	16.00 ± 9.92	−0.09	0.931

Among the 21 nonresponder patients, we did not identify significant acoustic difference between patients with only an improved RSI score and those with only an improved RFS.
Wilcoxon signed-rank test.
Abbreviations: Hz, Hertz; L, liter; NHR, Noise Harmonic Ratio; s, second; SPI, Soft Phonation Index; sPPQ, Smoothed Pitch Perturbation Quotient; VTI, Voice Turbulence Index; Z, statistic difference.

DISCUSSION

LPRD is a causative factor of chronic laryngitis and hoarseness. Since two decades, various studies investigating the pathophysiological mechanisms underlying the deterioration of voice quality in LPRD yielded unclear conclusions. To study the clinical evolution of patients under treatment, Belafsky et al developed RSI and RFS.[15,16] Since then, these two scales have been widely used for diagnosis and follow-up in many studies that observed significant improvement after treatment, which is similar to our study.[3,21] In contrast, we did not find significant improvement of some signs (especially granulations and subglottic edema) that could be explained by a different time of healing. In the present study, we also showed that nonresponder patients presented more tongue tonsil hypertrophy and significantly stronger scores of granulations compared with responder patients. These findings suggest that tongue tonsil hypertrophy and granulations could be severity signs of LPRD associated with increased resistance to empirical treatment. Similar findings were observed by DelGaudio et al who

TABLE 8.
Correlation Study (*P* Values) Between Perceptual Voice Quality Items and Acoustic Parameters in LPRD Patients

	Probant acoustic cues LPRD patients										
Blinded experienced judges	Jita	Jitt	RAP	PPQ	PFR	STD	vF0	ShdB	Shim	APQ	vAm
Grade	0.171	0.551	0.454	0.577	0.242	0.233	0.188	0.711	0.643	0.732	0.897
Roughness	0.192	1,000	0.836	1,000	0.447	0.511	0.393	0.67	0.622	0.636	0.684
Breathing	0.044	0.005	0.005	0.005	0.001	<0.001	0.001	0.214	0.221	0.23	0.350
Asthenia	0.526	0.021	0.030	0.021	0.131	0.037	0.103	0.875	0.922	0.953	0.891
Strain	0.205	0.956	0.805	0.985	0.586	0.526	0.449	0.841	0.827	0.798	0.742
Instability	0.82	0.495	0.526	0.495	0.778	0.383	0.563	0.438	0.466	0.715	0.576

The *P* values available in this table were calculated using Pearson correlation test.
jita = absolute jitter; ShdB: absolute shimmer.

demonstrated a continuum of increasing pharyngeal reflux with increased tongue tonsil hypertrophy.[19] Moreover, it is probable that granulation score is an indirect sign of chronic LPR involving macroscopic and microscopic changes of the laryngeal (vocal folds) mucosa that leads to chronic dysphonia. Thus, some nonresponder patients could have a long LPR history that needs more aggressive therapy and more time to cure (>6 months). Moreover, in our study, we had 10% of patients with OSA, which is known to be associated with LPRD and tongue tonsil hypertrophy.[22] This association underlies the interest to detect OSA in patients with both LPRD and tongue tonsil hypertrophy.

The real impact of diet and behavioral changes on symptoms has been the subject of some studies. Thus, Fass et al found that the use of PPIs without implementation of diet and lifestyle changes did not result in significant differences in treatment outcomes such as LPR patient-based questionnaire or acoustic measurements, yielding the interpretation of the diet effect difficult.[10] In this study, using a 10-point scale, we identified a positive effect of the adherence to diet regimen and lifestyle changes on the clinical symptoms, especially on the main causes of LPRD consultation. Indeed, the main identified correlations with the adherence to the regimen concern globus, throat clearing, troublesome cough, and heartburn account for 50% of the consultation motifs. This positive observation was not observed with signs. The regimen represents an important component of the efficiency of the treatment.[18] Thus, a suggestion's effect, a kind of placebo effect, could characterize patients who adhered to the regimen since they perceived a better improvement of their main symptoms. The existence of a placebo effect in the LPRD treatment has long been suggested but is not completely understood.[23] Our results could enrich the disparate knowledge on the subject.

In addition, elderly patients complained of less pyrosis that is attributed to the atypical clinical presentation related to aging following the degeneration of neurologic system.[24] Another relationship concerns the pyrosis sensation and the presence of endolaryngeal mucus. As suggested in other studies, the reflux of stomach contents in the distal portion of esophagus could activate vagal reflexes by the stimulation of the chemoreceptors and induce endolaryngeal mucus hypersecretion and throat clearing.[13]

In this study, we identified significant improvement of VHI components after treatment in LPRD patients irrespective to the therapeutic response. Sereg-Bahar et al reported similar results in each VHI component after PPI therapy.[23] Similarly, the patients of the study by Siupsinkiene et al reported a substantial decrease of their VHI scores after 3 months of omeprazole, suggesting the interest to use VHI as treatment voice quality outcome.[25]

Perceptually, we observed a significant improvement of the grades of dysphonia and roughness after therapy in responder patients. These results are partially consistent with the results of Park et al[12] that is, with the present study, the only trial that assessed the evolution of the perceptual voice quality of LPRD patients under treatment using a blind jury. The lack of improvement in nonresponder patients could be associated with the reduced clinical improvement of this patient group.

Concerning the impact of LPR on quality of life, we observed a significant improvement of each domain of SF-36 after treatment in responder patients, while in nonresponder patients, the improvement was low. These findings supported the observations of Lee et al who reported an increase of each SF-36 domain after treatment in a homogenous cohort of patients.[7] A few publications using other quality of life tools provided similar results.[9,25] SF-36 scorings correlated with the scores of VHI categories, suggesting an impact of the voice alterations in the general quality of life impairment.

Finally, our study was dedicated to the aerodynamic changes after treatment. We did not observe substantial improvement of PQ and MPT after treatment but only a trend of improvement of MPT in responder patients. Hamdan et al[11] and Wan et al did not observe significant enhancement of MPT after therapy in a recent prospective study.[21] With regard to the statistical trend found in the present study, it is possible that LPRD treatment could improve some aerodynamic measurements but further studies with a large number of patients are needed.

Acoustic measurement is another method to study subtle voice changes that are typically difficult to detect by the subjective assessment of the clinician or the patient himself/herself. Our acoustic study exhibited improvement of many F0 and intensity perturbation measurements, including Jitt, RAP, PPQ, Shim, sAPQ, APQ, and vAm in responder patients but no in nonresponder subjects, that partly supports the results of Jin et al who found significant changes in Jitt, Shim, and harmonics-to-noise ratio at 3 months posttherapy.[3] In their prospective study, Shaw et al demonstrated that hoarse patients with suspected LPRD had significant changes in Jitt and Shim after 12 weeks of combined omeprazole, gaviscon, and cisapride treatment.[8] Other studies reported mixed results.[9,26] The mixed results found in the literature are probably related to the myriad of methods used to measure the acoustic parameters; and the related impact of method on final results.[27] Indeed, it has been demonstrated that the potential effect of the treatment may or may not be statistically demonstrated depending on the selection of the time interval over which the acoustic parameters are measured.[9,27] That is why our acoustic analyses were conducted on three sustained vowels, which represent a better description of the patient's voice. We did not measure acoustic cues on a selected segment of one vowel that is more subject to variability.

As reported in recent paper, a current debate in LPRD exists concerning the link between clinical improvement and the improvement of voice quality. Both may evolve concomitantly or separately.[27] Interestingly, we observed that nonresponder patients complained more of dysphonia at baseline than responder patients. Their improvements in some voice quality outcomes, such as acoustic parameters, were also lower than responders. Thus, our study may

suggest that patients with substantial clinical improvement of signs and symptoms simultaneously improved their voice quality. Nevertheless, the evolution of acoustic parameter values could depend on the age of the patients. Indeed, as previously described,[24] the aging voice could impact the acoustic results, which underlies the need to conduct further studies interesting to the use of these outcomes according to the age.

To complete our study on the pathophysiological mechanisms underlying the voice quality alterations in LPRD, we conducted correlation studies among signs, perceptual and acoustic assessments. First, we identified a positive correlation between the perception of breathy voice and F0 perturbation cues. The traditional observed positive correlations in the current literature concerned roughness, jitter, breathiness, and shimmer.[29] Our atypical results could be explained by the ambiguous relation between the perceptual evaluation of both roughness and breathiness given that Millet and Dejonckere revealed that the presence of a breathy component in an impaired voice could negatively influence the perceptual assessment of roughness and vice versa.[28] Thus, the judgment of our three experienced speech therapists could be biased by the influence of one of the other components on the results of the other. Concerning the study of the correlation between videolaryngostroboscopic signs and acoustic parameters, we did not identify a statistically positive correlation between vocal fold edema and any acoustic measurements. Similar findings were reported in the study of Jin et al, which together with our publication are the only trials that studied the correlation between signs and objective voice quality measurements.[3] These results contradict the notion that vocal fold edema is the causative factor of the irregular vocal fold vibration, leading to hoarseness. Thus, our results suggest that voice impairment in LPRD could be due to other mechanisms, which could consist of the association of several observable and unobservable findings including dryness, microtraumatism, thickening and keratosis of the margin of the vocal folds, ulcerations, granulomas, and inflammatory modifications of the Reinke space. These mechanisms may cause an impairment of the vibratory process of the margin of the vocal folds that leads to aerodynamic and acoustic alterations. If we do not exclude the involvement of vocal folds edema in the development of voice impairment, especially in severe LPRD, our results suggest that it did not correspond to the main pathophysiological mechanism in the high majority of patients. We suggest that the difficulty to objectify some of these lesions with classical videolaryngostroboscopy examination could explain the reported discrepancies regarding the relationship between the improvement of symptoms, signs, and voice quality.[29]

CONCLUSION

Our report highlights the interest to use voice quality measurements (especially intensity and F0 short-term perturbation parameters) as subtle indicators of the efficiency of lifestyle changes, diet, and medical treatment in suspected LPR patients. They can highlight subtle changes in the patient's voice quality through the treatment. Further controlled international trials with larger cohorts are needed to develop better diagnosis criteria and stratification of LPRD patients following the severity of the disease.

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