Voice Quality as Therapeutic Outcome in Laryngopharyngeal Reflux Disease: A Prospective Cohort Study

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Abstract: Purpose. To study the usefulness of voice quality as therapeutic outcome in laryngopharyngeal reflux disease.

Material and methods. A total of 80 patients with reflux finding score (RFS) > 7 and reflux symptom index (RSI) > 13 were treated with pantoprazole, diet, and lifestyle recommendations for 3 months. The therapeutic effectiveness was assessed with RSI; RFS; Voice Handicap Index; blinded Grade, Roughness, Breathiness, Asthenia, Strain, and Instability (GRBASI); aerodynamic and a panel of acoustic measurements before and after treatment. A correlation analysis between symptoms, videolaryngostroboscopic signs, and acoustic measurements was conducted.

Results. Compared to baseline, means of RSI, RFS, Voice Handicap Index, perceptual dysphonia, and roughness significantly decreased. Significant improvements of phonatory quotient, percent jitter, percent shimmer, Relative Average Perturbation, Pitch Perturbation Quotient, Phonatory F0 Range, Amplitude Perturbation Quotient, smooth Amplitude Perturbation Quotient, and Peak-to-Peak Amplitude Variation were found at the end of treatment. Studies of correlation did not identify relevant correlation between videolaryngostroboscopic signs, especially vocal folds edema, and objective voice quality evaluations.

Conclusion. Voice quality assessments can help to better understand voice disorders and can be used as indicators of the treatment effectiveness in patients with laryngopharyngeal reflux-related symptoms.

Key Words: Laryngopharyngeal−Reflux−Laryngitis−Voice−Acoustic.

INTRODUCTION

Laryngopharyngeal reflux (LPR) is the back flow of gastric contents into the laryngopharynx where it comes in contact with the tissues of the upper aerodigestive tract.[1] Ten percent of outpatients visiting Ear, Nose, and Throat (ENT) departments would be concerned[2,3] and LPR is involved in up to 75% of patients with refractory ENT symptoms.[4] Common symptoms include globus pharyngeus, throat clearing, and hoarseness. The latter is noted in 71 to 79% of patients[5,6] and typically affects patient's quality of life by the development of a communicative handicap.[7] The usual signs related to LPR are posterior commissure hypertrophy, hyperemia, and diffuse laryngeal edema.[5] For two decades, many authors studied voice quality alterations in LPR patients, particularly the use of voice quality assessments as therapeutic outcomes. Some studies identified objective voice quality, precisely acoustic measurements, as useful in the treatment follow-up,[3,8,9] while other did not find significant improvement along the treatment.[10] Thus, controversial results persist particularly due to methodological discrepancies between studies concerning the method used to measure acoustic parameters.[9,11] Moreover, none of these studies have studied voice quality with a complete assessment including at least, subjective, aerodynamic, and acoustic measurements.

The aims of this study are to investigate the usefulness of voice quality as therapeutic outcome in LPR patients who benefited from an empirical therapeutic trial, and to compare voice quality evolution with symptoms, signs, and quality of life evolutions throughout the treatment.

MATERIALS AND METHODS

Subject recruitment

Eighty patients with LPR-related symptoms (ie, hoarseness, globus sensation, throat clearing, throat pain, odynophagia, dysphagia, cough, heartburn, and regurgitation) were recruited at the Otolaryngology—Head and Neck Surgery Departments of both EpiCURA Hospital and Liege University Hospital (study protocol ref. 2015/99-B707201524621). After a clinical ENT examination, Reflux symptom score (RSI > 13) and reflux finding score (RFS > 7) were used to diagnose LPR according to the thresholds described by Belafsky et al, which were associated with a positive double-probe pH monitoring result.[12,13] RFS score was assessed in a blind manner as detailed below. With regard to an American management protocol of LPR disease,[14,15] 24-H pH impedance metry

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was only used for the diagnosis of nonresponder patients after empirical treatment. Nonresponder subjects were defined as patients who did not improve both RSI (≤ 13) and RFS (≤ 7) at the end of the empirical treatment. Among the 80 patients included in the present study, 59 exhibited a reduction of RSI and RFS below the threshold reference points at the end of treatment. Twenty-one patients were considered as nonresponder, and the LPR diagnosis was made using additional examinations. The clinical characteristics of patients are available in Table 1.

Exclusion criteria

Patients with cofactors able to bias the clinical and voice quality evaluations related to LPR were carefully excluded. These cofactors included vocal overuse (voice professionals), neurological disease affecting voice, psychiatric illness, upper respiratory tract infections within the last month, an antacid treatment already started or prior antireflux surgery, previous history of cervical surgery or radiotherapy, laryngeal trauma, vocal cord paralysis/paresis, benign vocal fold lesions, pharyngolaryngeal malignancy, active seasonal allergies, asthma, chronic obstructive pulmonary disease, PPIs hypersensitivity, active smokers, alcoholics, pregnant, and lactating women. Some of the patients included in this study have been studied in another published study.[16]

TABLE 1.
Clinical Characteristics of Patients

LPR Patients		
	Total (80)	%
Mean age (y)	51.3	–
BMI (kg/m^2)	26.36	–
Gender (M/F)	40/40	50/50
Adverse reactions	0	0
Main complaints		
Globus sensation	16	20%
Dysphonia	16	20%
Cough	11	13.75%
Odynophagia	9	11.25%
Heartburn	7	8.75%
Throat clearing	6	7.5%
Dysphagia	5	6.25%
Sticky expectorations/xerostomia	4	5.00%
Postnasal drip	3	3.75%
Otalgia	1	1.25%
Dyspepsia	1	1.25%
Breathing difficulties	1	1.25%
All complaints		
Throat clearing	76	95%
Dysphonia	68	85%
Heartburn	69	86%
Postnasal drip/ Sticky expectorations	63	79%
Cough	62	78%
Globus sensation	61	76%
Cough after eating/lying down	47	59%
Breathing difficulties	46	58%
Dysphagia	41	51%

BMI, body mass index; LPR, laryngopharyngeal reflux; y, years.

Management and treatment protocol

To improve patient care, we used a clinically validated protocol for the management of the LPR patients throughout the therapeutic trial (Figure 1).[14,15] Thus, the empirical therapeutic trial consisted of diet, lifestyle changes, and twice-daily proton pump inhibitors (PPIs, 20 mg pantoprazole 2/d) for 3 months.

Clinical evaluations, subjective voice assessments, and quality of life

Patients were evaluated along the empirical therapeutic trial with RSI and RFS. RFS was evaluated by an experienced laryngologist (MK) using videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) in a blind manner in regard to the patient complaints (RSI). Patients completed the Voice Handicap Index (VHI) and the Short Form 36 Health Survey (SF36) at baseline and after treatment.

The perceptual voice quality of hoarse LPR patients was performed by a jury of experienced listeners (three experienced speech therapists with demonstrated[17] good intrarater and inter-rater reliabilities). They used Grade, Roughness, Breathiness, Asthenia, Strain, and Instability scale (GRBASI scale). Patients read a balanced text during the consultation, and the related recordings were available for the judges at the end of the study. Each listener rated the perceptual voice quality on this text in a blind manner according to the state of the patient (baseline, posttreatment). In fact, listeners did not know if the recording was pre- or posttreatment time. Experts assessed voice samples in a quiet place within a few days. Patient management is described in Figure 1.

Aerodynamic and acoustic measurements

Aerodynamic assessments consisted of an evaluation of the maximum phonation time (MPT), phonatory quotient (PQ), and slow vital capacity (VC, to calculate PQ) with a calibrated spirometer (Spiro-USB100; Medical Electronic Construction, Brussels, Belgium). MPT was recorded three times, and we considered the best value for the study.

The same practitioner (JRL) performed voice recordings 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. To measure acoustic cues, patients were asked to produce three times the sustained vowel /a/, holding the utterance as long as possible. Acoustic parameters were measured on the entire signal of the three vowels (excluding the first and last unstable milliseconds of the signal) using MDVP software (KayPentax, NJ, USA). To identify the most interesting

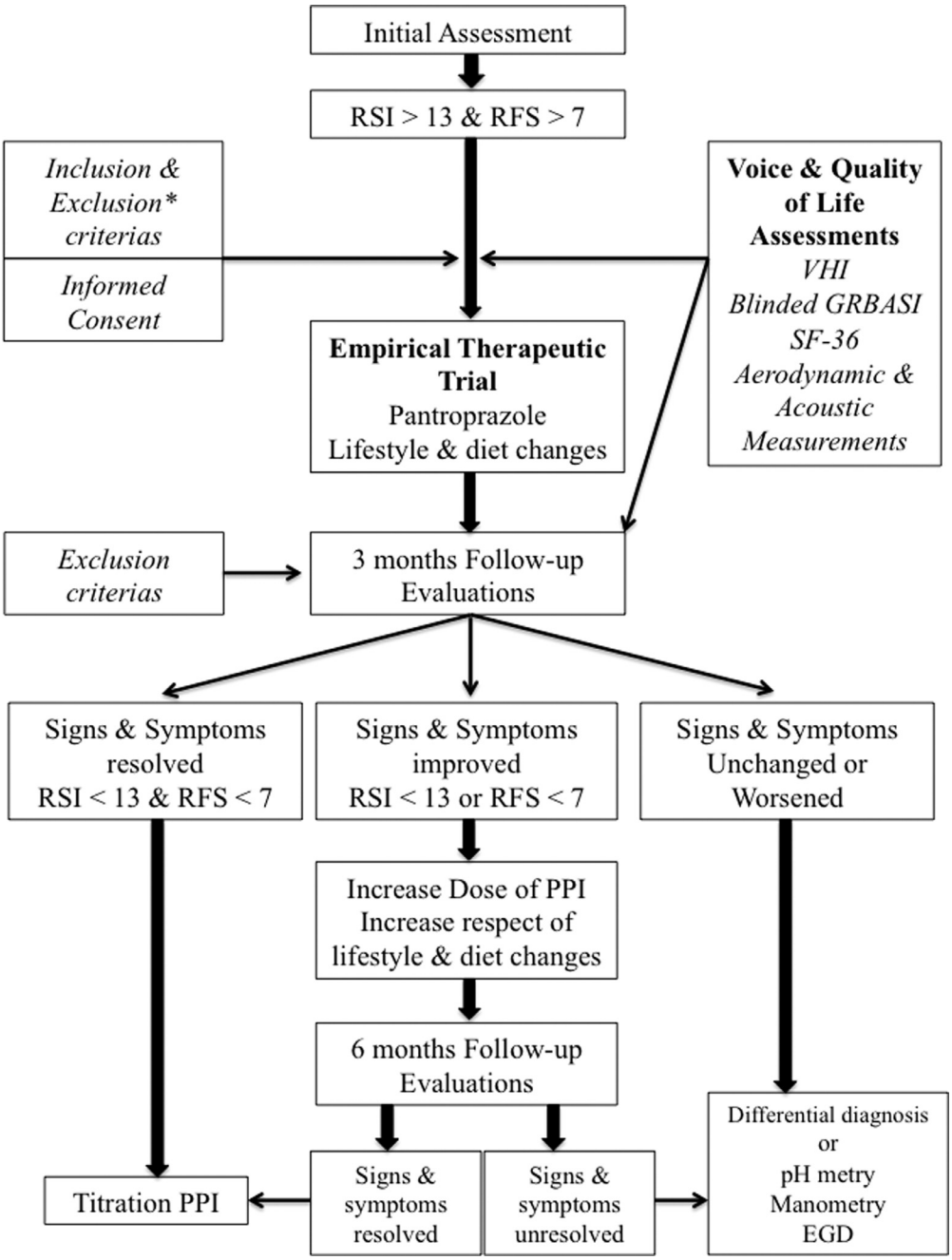

FIGURE 1. Flow chart describing the algorithm for assessment and management of patients. Patients with LPRD symptoms (RSI > 13) and signs (RFS > 7) were recruited and assessed at baseline and treated by PPIs and diet advices during 3 months. A second clinical and voice quality assessment was made after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

parameters for the evaluation of treatment efficiency, we measured the following parameters: Fundamental frequency (F0), Mean F0, maximum F0 (Fhi), minimum F0 (Flo), Standard Deviation of F0 (STD), Fundamental frequency variation (vF0), percent jitter (Jitt), Relative Average Perturbation (RAP), Pitch Perturbation Quotient (PPQ), Smoothed Pitch Perturbation Quotient (sPPQ), Phonatory Fundamental Frequency Range (PFR), percent shimmer (Shim), Amplitude Perturbation Quotient (APQ), Smoothed Amplitude Perturbation Quotient (sAPQ), Peak-to-Peak Amplitude Variation (vAm), Noise Harmonic Ratio (NHR), Voice Turbulence Index (VTI), and Soft Phonation Index (SPI).

To better understand the relationship between videolaryngostroboscopic symptoms, signs, and objective voice quality, we performed a correlation analysis between components of RSI, RFS, aerodynamic, and acoustic measurements.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS version 22.0; IBM Corp. Armonk, NY). Changes in RSI, RFS, VHI, GRBASI, SF-36 scores and the effect of treatment on aerodynamic and acoustic measurements were calculated using the Wilcoxon signed-rank test. Correlation analysis was made using Spearman correlation test. A level of significance of 0.05 was adopted.

RESULTS

Clinical evolution and correlations

Significant improvement in RSI and RFS scores was found at 3 months of treatment. Therefore, except for subglottic edema that was rarely found in our cohort, the values of each RFS and RSI component significantly improved after treatment (Table 2). Our correlation analysis between RFS and RSI revealed several notable correlations. According to Spearman's analysis, we observed positive relationship between the pyrosis sensation and the presence of endolaryngeal mucus ($P = 0.044$) and negative correlation between the patient's age and the pyrosis sensation ($P = 0.003$).

Subjective voice quality

The values of VHI components significantly decreased after treatment (Table 3). With regard to perceptual voice quality, the blinded ratings of our three judges exhibited a significant improvement of dysphonia, roughness, and strain from baseline to the end of treatment.

Quality of life assessment

The scorings of each item of SF-36 reported a significant improvement after treatment (Table 4). We identified a myriad of significant correlations between VHI and SF-36 components as described in Table 5.

Aerodynamic and acoustic measures

The mean values of MTP and PQ significantly improved after treatment (Table 6). According to Spearman's correlation test, we identified significant positive relationships between the reduction of MPT and both the severity of throat clearing ($P = 0.035$) and breathing difficulties score ($P = 0.038$).

Many frequency and intensity short-term perturbation parameters significantly improved after treatment. The mean values of Jitt, RAP, PPQ, Shim, APQ, and sAPQ significantly decreased at the end of the treatment. Among F0 and intensity mid-term perturbation cues, only the mean values of PFR and vAm significantly decreased at the end of the empirical therapeutic trial (Table 6).

We did not find significant correlation between vocal folds edema and all acoustic measurements. Among acoustic parameters that significantly improved along treatment, significant positive correlations were found between breathiness and jitt, RAP, PPQ ($\rho = 0.510$; $P = 0.005$), PFR ($\rho = 0.510$; $P = 0.001$), STD ($\rho = 0.620$; $P = 0.001$), and vF0 ($\rho = 0.510$; $P = 0.001$; Spearman correlation test).

DISCUSSION

LPR disease has long been identified as a causative factor of chronic laryngitis.[18] Since Koufman's first works,[1,6,18] many

TABLE 2.
Pre- and Posttreatment Clinical, Subjective Voice and Quality of Life Assessments in Clinically Diagnosed LPRD Patients

	Clinically Diagnosed LPR Patients			
Scales	Pretreatment	Posttreatment	Z	*P* Value
RSI	22.03 ± 6.78	8.93 ± 6.13	−7.64	<**0.001**
Voice problem	2.71 ± 1.71	1.29 ± 1.28	−4.92	<**0.001**
Throat clearing	3.63 ± 1.72	1.78 ± 1.48	−5.91	<**0.001**
Postnasal drip	2.73 ± 1.88	1.25 ± 1.45	−5.29	<**0.001**
Dysphagia	1.35 ± 1.62	0.46 ± 1.04	−4.12	<**0.001**
Coughing posteating & lying down	1.95 ± 1.97	0.65 ± 1.21	−4.90	<**0.001**
Breathing difficulties	1.54 ± 1.71	0.62 ± 1.16	−4.26	<**0.001**
Troublesome cough	2.44 ± 1.88	0.73 ± 1.07	−5.87	<**0.001**
Globus pharyngeus	2.65 ± 1.93	1.06 ± 1.46	−5.92	<**0.001**
Pyrosis, heartburn & chest pain	3.06 ± 1.84	1.05 ± 1.40	−6.49	<**0.001**
RFS	10.65 ± 2.38	4.88 ± 3.16	−7.68	<**0.001**
Subglottic edema	0.06 ± 0.33	0.01 ± 0.01	−1.63	0.102
Ventricular obliteration	1.10 ± 1.42	0.56 ± 1.11	−3.19	**0.001**
Arytenoid/diffuse redness	3.05 ± 1.05	1.44 ± 1.20	−6.11	<**0.001**
Vocal folds edema	1.26 ± 0.79	0.39 ± 0.56	−5.98	<**0.001**
Diffuse laryngeal edema	1.16 ± 0.97	0.47 ± 0.73	−4.63	<**0.001**
Posterior commissure hypertrophy	2.13 ± 0.68	1.18 ± 0.83	−6.39	<**0.001**
Granuloma/Granulation	0.56 ± 0.90	0.28 ± 0.70	−2.54	**0.011**
Endolaryngeal mucous	1.33 ± 0.95	0.56 ± 0.90	−4.73	<**0.001**

LPR, laryngopharyngeal reflux; RFS, reflux finding score; RSI, reflux symptom index; Z, statistic difference.*Wilcoxon signed-rank test.

TABLE 3.
Pre- and Posttreatment Subjective Voice Quality of LPR Patients

	Clinically Diagnosed LPR Patients			
Scales	Pretreatment	Posttreatment	Z	*P* Value
VHI	18.30 ± 14.62	10.35 ± 9.98	−5.38	<**0.001**
VHIe	3.80 ± 4.78	2.14 ± 3.42	−3.85	<**0.001**
VHIp	9.91 ± 7.23	5.62 ± 5.22	−5.44	<**0.001**
VHIf	4.58 ± 4.89	2.58 ± 3.02	−3.89	<**0.001**
Grade	1.00 ± .76	0.62 ± 0.63	−2.43	**0.015**
Roughness	0.92 ± 0.66	0.62 ± 0.54	−2.56	**0.011**
Breathiness	0.36 ± 0.58	0.36 ± 0.63	−0.00	1.00
Asthenia	0.23 ± 0.23	0.36 ± 0.58	−1.67	0.096
Strain	0.79 ± 0.79	0.51 ± 0.64	−2.08	**0.038**
Instability	0.72 ± 0.72	0.44 ± 0.55	−1.85	0.065

LPR, laryngopharyngeal reflux; VHIe/p/f, voice handicap index emotional, physic, functional; Z, statistic difference.*Wilcoxon signed-rank test.

authors studied pathophysiological mechanisms underlying hoarseness related to LPR, yielding unclear conclusions. To improve the management of LPR patients, Belafsky et al developed RSI and RFS in 2001.[12,13] Nowadays, these two questionnaires are widely used around the world and substantially improved the assessment of both signs and symptoms along the therapeutic trial. Overall, although they are still incomplete with missing symptoms and signs, a large number of studies identified significant improvements of RSI and RFS items after treatment, which is similar to our results.[3,7,9,19,20] The lack of improvement of subglottic edema is probably due to the low number of patients exhibiting this sign at baseline. As found in the current literature,[21] we did not find significant correlation between total scores of RSI and RFS. One hypothesis that might explain this result is that both RFS and RSI do not include respectively all LPR signs and symptoms. Indeed, some usual symptoms (ie, throat pain, halitosis, odynophagia), laryngeal and extralaryngeal signs (ie, keratosis, hypo- and oropharyngeal erythema, edema, coated tongue, and tongue tonsil hypertrophy) that are usually found in LPR disease[22-25] are not described in these two instruments. Moreover, some different symptoms such as heartburn, chest pain, indigestion, and regurgitations are grouped in one item in RSI that can lead to confusion in the interpretation of the patient's answer. In our correlation analysis between symptoms and signs, we observed positive relationship between the pyrosis sensation and the presence of endolaryngeal mucus ($P = 0.044$) that can be explained by an indirect effect of reflux of gastric contents in the distal esophagus. Indeed, as suggested in other studies,[26-28] 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. We also identified negative correlation between the patient's age and the pyrosis sensation ($P = 0.003$). We think that this last result mainly reflects that elderly patients complained of less pyrosis because degeneration of sensitive neurologic system.

With regard to the evolution of subjective voice quality, the mean value of all VHI components significantly decreased after treatment. Sereg-Bahar et al as well as

TABLE 4.
Pre- and Posttreatment Short Form 36 Health Survey Values of LPR Patients

SF36				
Physical Functioning	81.32 ± 19.19	85.44 ± 18.28	−2.92	0.004
Role-Physical	62.87 ± 37.53	75.37 ± 32.47	−2.88	0.004
Bodily Pain	69.21 ± 29.59	79.50 ± 25.28	−3.08	0.003
General Health	58.79 ± 17.67	65.81 ± 16.65	−3.65	<0.001
Vitality	52.66 ± 20.34	62.59 ± 19.709	−4.07	<0.001
Social Functioning	74.72 ± 26.66	86.09 ± 17.39	−3.40	0.001
Role-Emotional	70.53 ± 39.76	85.75 ± 29.62	−3.62	<0.001
Mental Health	60.85 ± 21.08	69.59 ± 18.46	−4.56	<0.001
Physical Health	68.05 ± 20.44	76.53 ± 17.72	−4.34	<0.001
Mental Health	64.69 ± 21.59	76.00 ± 17.28	−5.64	<0.001

LPR, laryngopharyngeal reflux; SF36, Short Form 36 Health Survey; Z, statistic difference.*Wilcoxon signed-rank test.

TABLE 5.
Correlation Study Between SF-36 and VHI Scores in Clinically Diagnosed Patients

	LPR Patients			
SF36 Scores	VHI Tot	VHIf	VHIe	VHIp
Physical functioning	−0.192	−0.249*	−0.185	−0.132
Role-Physical	−0.245*	−0.319†	−0.303*	−0.108
Bodily pain	−0.303*	−0.322†	−0.182	−0.281*
General health	−0.136	−0.193	−0.100	−0.121
Vitality	−0.171	−0.090	−0.192	−0.170
Social functioning	−0.303*	−0.294*	−0.283*	−0.234
Role-Emotional	−0.098	−0.100	−0.123	−0.048
Mental health	−0.097	−0.043	−0.187	−0.075
Physical health	−0.287*	−0.372†	−0.281*	−0.188
Mental health	−0.209	−0.189	−0.244*	−0.157

* *P* value <0.05.
† *P* value <0.01.
LPR, laryngopharyngeal reflux; SF36, Short Form 36 Health Survey; VHIe/p/f, voice handicap index emotional, physic, functional; Z, statistic difference.The coefficients available in this table were calculated using Spearman's correlation test.

Siupsinskiene et al reported similar results in each VHI component after a 3 months PPIs therapy.[29,30] Evaluating the perceptual voice quality with three experienced speech therapists, we found significant improvements of dysphonia, roughness, and strain at the end of treatment that partially corroborates the results of Park et al who also assessed the evolution of the perceptual voice quality of LPR patients with a blind jury.[31] Moreover, one of the objectives of our study was to globally assess the LPR alterations of the quality of life and the potential relation with VHI. Thus, we observed pejorative scores of each domain of SF-36 at baseline and significant improvement of each after treatment. Lee et al also observed low values of SF36 in LPR patients and substantial improvement after PPIs treatment, but they did not study the potential relationship with voice quality impairment and LPR symptoms.[7] Many other studies reported that LPR patients had quality of life impairments at baseline and significant improvement along treatment.[32,33] Moreover, Gong et al observed that the severity of LPR symptoms was related to decreased health-related quality of life.[34] In our correlation analysis, we formally identified positive correlations between SF-36 scorings and the scores of VHI categories. The relationship between these two quality-of-life instruments may suggest that the development of hoarseness, and the related increase of VHI scores (communicative handicap) can alter the overall quality of life of patients. In other words, the hoarseness that leads to the communicative disability could be a key symptom in the health quality of life impairment.

Regarding objective voice quality assessments, we found substantial improvement of PQ and MPT from baseline to the end of treatment. In a prospective uncontrolled trial, Hamdan et al did not observe similar improvement of MPT but the duration of treatment was 4 weeks that can be insufficient to observe significant improvements of MPT.[10] Moreover, lung capacities, especially the slow vital capacity, were not used to measure PQ, limiting our comparison. Acoustically, we identified significant improvement of many F0 and intensity perturbation measurements, including Jitt, RAP, PPQ, PFR, Shim, APQ, sAPQ, and vAm. The acoustic results of our study partly corroborate those of two main studies. First, Jin et al identified significant improvements in Jitt, Shim, and HNR values at 3 months posttreatment.[3] Second, Shaw et al demonstrated significant improvements in Jitt and Shim values after 3 months of PPIs, gaviscon, and cisapride treatment.[8] The other studies that used acoustic parameters to assess the therapeutic effectiveness in LPR disease reported controversial results.[10,35] However, it is important to keep in mind that our results should be cautiously compared with the literature given the myriad of methods used for the measurement of acoustic parameters, and the impact of the related methods on the final results.[9,11] Indeed, in a previous acoustic study, the evolution of acoustic measurements throughout treatment (same patients and same voice samples) has been compared regarding the portion choice (mid-production, most stable interval) and the time interval of the voice samples on which acoustic measurements have been measured.[11] The results exhibited 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.[11] With regard to these results, we have measured acoustic parameters on the entire signal of three sustained vowels to have "the most representative" measurement of the patient voice.

To better understand the pathophysiological mechanisms underlying hoarseness related to LPR disease, we realized a correlation study between videolaryngoscopic signs and objective voice quality measurements. We did not identify significant positive correlation, especially between vocal fold edema and acoustic parameters. With the study of Jin et al,[3] these results contradict the widespread notion that vocal fold edema is the causative factor of hoarseness in LPR disease. We believe that the pathophysiological mechanisms underlying the occurrence of hoarseness in LPR disease are more complicated. Indeed, as summarized in a multifactorial model,[24] the hoarseness related to LPR could be the result of macro and microscopic changes of the vocal folds including dryness, microtraumatism and keratosis of the margin of the vocal folds, thickening of the epithelium, ulcerations, granulomas and inflammatory modifications of the Reinke space.[24] These changes could be associated with modifications of the biomechanical properties of the vocal folds that impact the vibratory process and voice quality. Naturally, edema of the vocal folds can occur in LPR patients but, based on the results of this study, we believe that this sign is not the main cause of hoarseness related to LPR. With regard to PQ and

TABLE 6.
Pre- and Posttreatment Aerodynamic and Acoustic Measurements in Clinically Diagnosed LPR Patients

		LPR Patients			
Aerodynamic Measurements	Units	Pretreatment	Posttreatment	Z	*P* Value
MPT	s	15.01 ± 7.63	16.51 ± 7.54	−2.30	**0.021**
PQ	mL/s	275.53 ± 120.30	250.37 ± 97.50	−2.12	**0.034**
Acoustic Parameters					
Fundamental frequency					
F0	Hz	156.47 ± 45.52	155.84 ± 42.60	−0.19	0.849
MF0	Hz	155.14 ± 45.52	154.22 ± 42.11	−0.42	0.674
Fhi	Hz	180.79 ± 55.46	175.85 ± 51.76	−1.05	0.296
Flo	Hz	138.66 ± 41.30	139.99 ± 38.14	−1.23	0.218
F0 short-term perturbation cues					
Jitt	%	2.63 ± 1.50	2.39 ± 2.22	−2.87	**0.004**
RAP	%	1.56 ± .89	1.42 ± 1.29	−2.85	**0.004**
PPQ	%	1.59 ± .95	1.46 ± 1.52	−2.87	**0.004**
sPPQ	%	2.45 ± 1.92	2.31 ± 2.55	−1.63	0.104
F0 mid-term perturbation cues					
PFR		5.33 ± 2.92	4.71 ± 2.72	−2.10	**0.036**
STD	Hz	7.51 ± 7.49	6.70 ± 9.21	−1.58	0.113
vF0	%	4.54 ± 3.94	4.05 ± 4.30	−1.62	0.606
Intensity short-term perturbation cues					
Shim	%	7.17 ± 2.98	6.63 ± 3.36	−2.51	**0.012**
APQ	%	5.65 ± 2.64	5.23 ± 2.66	−2.36	**0.018**
sAPQ	%	9.77 ± 3.12	8.75 ± 2.89	−2.71	**0.007**
Intensity mid-term perturbation cues					
vAm	%	16.35 ± 4.80	14.59 ± 4.88	3.29	**0.001**
Noise-related measurements					
NHR		0.19 ± 0.06	0.18 ± 0.09	−1.37	0.170
VTI		0.06 ± 0.06	0.07 ± 0.11	−0.09	0.926
SPI		17.80 ± 7.60	16.98 ± 8.52	−1.25	0.209

μs, μsecond; dB, decibels; Hz, Hertz; L, liter; LPR, laryngopharyngeal reflux; MPT, maximal phonation time; PQ, phonatory quotient; s, second; ml/s, milliliter/second; Z, statistic difference.The abbreviations of acoustic parameters are described in the manuscript.*Wilcoxon signed-rank test.

shimmer, the alteration of these two measurements could be related to subglottal pressure disorder. Physiologically, to have stability in the voice intensity, the laryngeal airflow must be continuous and the free edge of the vocal folds (and the related biomechanical properties) must be intact. LPR can alter both the lung function (bronchial sensitivity) and the integrity of vocal folds that can lead to PQ and shimmer impairments. This hypothesis could be confirmed in future studies with a measurement of estimated subglottal pressure and voice intensity before and after treatment.

This study is characterized by several weaknesses. First, many aerodynamic measurements (estimated subglottic pressure, voice intensity, etc.) were not used, although they would have improved our understanding of the pathophysiological mechanisms underlying the development of hoarseness. Second, using RFS, we focused on laryngeal signs described in the instrument, and we did not assess other important signs that can be involved in the development of hoarseness such as keratosis, ulcerations, thickening of the epithelium of the vocal folds, etc. Concerning the LPR diagnosis, we did not systematically use pH impedance monitoring at baseline in all patients 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.[36,37] Similarly, an increasing number of authors consider the response of symptoms to behavioral and empirical medical treatment as a reliable alternative approach to the pH impedance metry to confirm the diagnosis.[14,15] However, Wan et al compared these two approaches and concluded that they are quite competitive in the selection of LPR patients.[38] Third, as recently demonstrated,[39,40] age and gender of LPR patients may impact the results of the voice quality evolution. Future studies with a large number of patients are needed to specify the usefulness of acoustic parameters according to both age and gender. Fourth, we should keep in mind that in the present study, the mean values of pretreatment VHI and GRBASI scores were low in comparison with some previous studies.[7,13] It is possible that a large number of LPR patients in our cohort had mild and moderate dysphonia. In fact, in comparison with other countries, Belgium has an accessible health care system and that is easy to have a quick appointment in otolaryngology. We suggest that most of our patients have consulted early after the onset of the disease and they have few chronic

macroscopic and microscopic modifications of the vocal folds and low dysphonia. This possibility should take into consideration for the future comparison of our data with other studies.

CONCLUSION

Voice quality measurements are interesting indicators of the efficiency of diet, lifestyle changes, and medical treatment in LPR. Further controlled international trials with larger cohorts are needed to better identify the mechanisms underlying the development of hoarseness in LPR disease.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jvoice.2018.08.018.

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