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Change of signs, symptoms and voice quality evaluations throughout a 3- to 6-month empirical treatment for laryngopharyngeal reflux disease

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Objective: To assess the usefulness of voice quality measurements as a treatment outcome in patients with laryngopharyngeal reflux (LPR)-related symptoms.

Design: Prospective uncontrolled multi-centre study.

Material and methods: A total of 80 clinically diagnosed LPR patients 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; blinded Grade, Roughness, Breathiness, Asthenia, Strain and Instability (GRBASI) and aerodynamic and acoustic measurements were evaluated at baseline, 3 months (n = 80), and 6 months (n = 41) post-treatment. We conducted a correlation analysis between the adherence to the diet, and the evolution of both signs and symptoms and between videolaryngostroboscopic signs and acoustic measurements.

Results: Reflux symptom index, RFS, perceptual voice quality evaluations (dysphonia, roughness, strain and instability), and aerodynamic and acoustic measurements (ie, percent jitter and percent shimmer) were significantly improved at 3 months post-treatment but not at 6 months. Percent jitter was the most useful outcome for evaluating the clinical evolution of patients throughout the treatment course. A significant relationship between globus sensation and posterior commissure hypertrophy was documented; both seemed to significantly improve from 3 to 6 months. The correlation analysis revealed correlations between adherence to diet recommendations and the improvement of symptoms and between posterior commissure granulation severity and acoustic measurement impairments.

Conclusion: Voice quality improved in a manner similar to both signs and symptoms throughout a 6-month empirical treatment with better improvement the 3 first months. Voice quality assessments can be used as indicators of treatment effectiveness in patients with LPR-related symptoms.

1 | INTRODUCTION

Laryngopharyngeal reflux (LPR) is the backflow of gastric contents into the laryngopharynx, where it comes in contact with the tissues

Study from LPR project of Young Otolaryngologist International Federation of Oto-rhino-laryngology Societies – Research Committee.

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of the upper aerodigestive tract.[1] LPR affects approximately 10% of outpatients who seek otolaryngology consultation[2,3] and 50%-80% of patients in voice centres.[4] The most frequent symptoms are globus sensation, throat clearing, cough, and hoarseness, the latter accounting for more than 80% of patients.[5,6]

To date, the LPR diagnosis remains controversial. Multichannel impedance and pHmetry studies do not seem to be a real gold standard because some evidence (ie, high false-positive and false-negative rates, interpretation difficulties, and inconsistency between pH findings and signs and symptoms) suggests that this method is not perfect.[7,8] Moreover, this approach is expensive and annoying for many patients. As a result, some American authors consider the response of symptoms and signs to empirical medical treatment as a reliable alternative approach for confirming the diagnosis.[9,10] This empirical approach is based on the utilisation of both the reflux symptom index (RSI > 13) and the reflux finding score (RFS > 7) at baseline, followed by treatment with dietary recommendations and proton pump inhibitors for a 3-month setup period.[9,10] This approach makes sense if there are adequate exclusion criteria in the selection of patients. Regarding the evolution of symptoms and signs, titration/increase of the PPI dose may be proposed for three additional months. The LPR diagnosis is only considered if the patient responds ("responder patients", RSI ≤ 13 & RFS ≤ 7) after 3 or 6 months of behavioural and medical treatment.[9,10] The diagnosis of non-responder patients remains uncertain and requires additional examinations, such as multichannel impedance and pHmetry studies.[9]

Another controversy concerns the evolution of voice quality throughout the treatment period. Indeed, since the first works of Koufman in the early 1990s, only some twenty trials have studied the development of voice impairments related to LPR and the use of voice quality assessments as outcome measures.[11,12] Some of these studies reported significant improvement in voice quality after medical treatment,[3,11,13] while others found mixed results.[14,15] As shown in a previous literature review, most of these studies focused on the evolution of voice quality throughout the first 3 months, but none studied voice quality after the first 3 months of treatment, especially throughout the empirical treatment.[12]

In this study, we aimed to analyse symptoms, signs, and voice quality changes throughout the 6-month course of empirical treatment and to examine the relationships among signs, symptoms, and voice quality in clinically diagnosed and confirmed LPR patients. We sought to assess the usefulness of voice quality assessments as a treatment outcome.

2 | MATERIALS AND METHODS

2.1 | Ethical considerations

The protocol of the study has been approved by the ethics committees of EpiCURA and CHU de Liege Hospitals (ref.2015/99 and ref. B707201524621).

Keypoints

- Objective voice quality assessment (especially phonatory quotient, jitter and shimmer) is an interesting indicator of the LPR treatment efficiency.
- There are few clinical and voice quality improvements after 3-months of treatment because only posterior commissure hypertrophy and globus sensation similarly improve from 3 to 6 months. However, the evolutions of globus sensation and posterior commissure hypertrophy are closely linked.
- The respect of the diet behavioural changes could improve the clinical complaints by, in part, a placebo effect.

2.2 | Subject characteristics

From September 2013 to April 2016, we recruited 122 patients from the Otolaryngology-Head & Neck Surgery Departments of EpiCURA and Liege Hospitals. RSI > 13 and 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. At baseline, our patients did not have double-probe pH monitoring. However, double-probe pH impedance monitoring was used for the diagnosis of non-responder patients after empirical treatment (positive if >3 episodes of pH < 4 at both proximal and distal probes).[16] We excluded patients with the following criteria: neurological disease affecting the voice, psychiatric illness, upper respiratory tract infections within the last month, antacid treatment (ie 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, rheumatological 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.

All patients were treated with diet and lifestyle behavioural changes and twice-daily proton pump inhibitors for 6 months (PPIs; 20 mg pantoprazole twice daily). Following the current clinically American validated protocol for the empirical management of LPR patients,[9,10] the treatment of responder patients (RSI ≤ 13 & RFS ≤ 7) was titrated (from 20 mg twice daily to 20 mg daily), and the therapy of low-responder/non-responder subjects was adapted (maintained/increased PPIs doses (from 20 mg twice daily to 40 mg twice daily)) after the three-first months (Figure 1). Patients who were not completely cured after 3 months were clinically assessed a second time at 6 months. With regard to some recommendations,[7,9,10] to confirm the diagnosis, non-responder patients received double-probe pH impedance monitoring. They stopped the PPIs

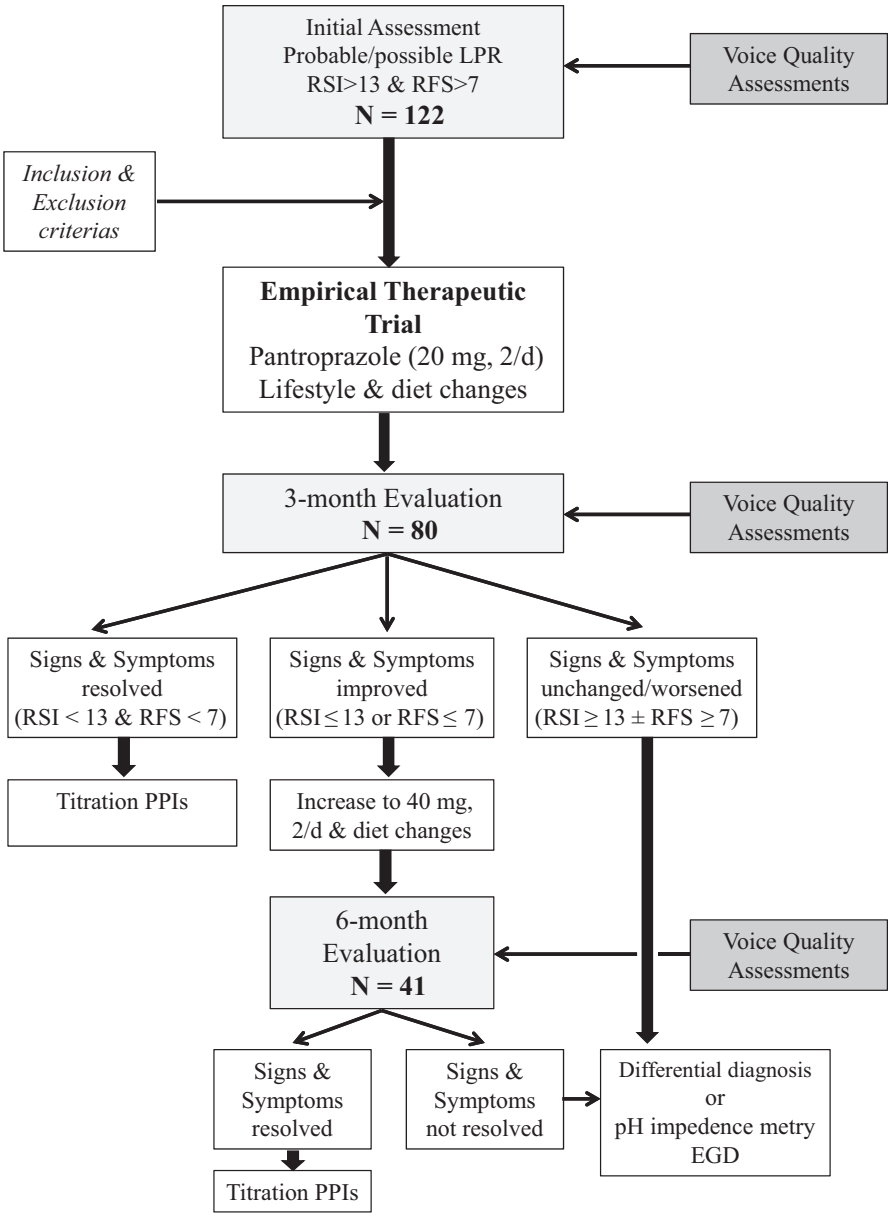

FIGURE 1 Flow chart describing the algorithm for the assessment and management of patients. Patients with LPR symptoms (RSI>13) and signs (RFS>7) were recruited and treated with PPIs and dietary advice for 6 months. The subjects were assessed at baseline and 3 and 6 months after the treatment initiation. pH/impedancemetry was mainly recommended for patients who did not respond to the empirical treatment

intake 1 month before the double-probe pH impedance monitoring. We did not realise pH impedance monitoring at baseline for all patients regarding the cost of the examination and because the use of RFS > 7 and RSI > 13 followed by empirical therapeutic trial as diagnosis method has been demonstrated as a competitive diagnosis method.[17] In this context, our approach represented a cost-effective approach.

According to recent publications,[10] we defined confirmed LPR diagnosis as the positive response to the empirical therapeutic course or the objectification of LPR with pH impedance metry (resistant patients).

Concerning the diet and lifestyle behavioural changes, the patients received personalised recommendations depending on their dietary habits in the form of a recommendation (validated) grid based on Koufman's work.[18] Adherence to these recommendations was evaluated by the patient throughout the therapeutic course using a point scale ranging from 0 (non-adherent) to 10 (fully adherent to the recommendations).

2.3 | Clinical evaluations and voice quality assessment

We recorded the severity of signs and symptoms throughout the treatment with RSI and RFS. RFS was evaluated using videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) in a blinded manner in response to patient complaints (RSI). Perceptual voice evaluations (Grade, Roughness, Breathiness, Asthenia, Strain and Instability (GRBASI scale)) of hoarse patients were performed by a jury of five experienced speech therapists who were blinded to the time of the recording.

Aerodynamic and acoustic assessments were conducted three times: at baseline and 3 and 6 months after the treatment initiation.

Maximum phonation time (MPT) and phonatory quotient (PQ) were measured using a calibrated spirometer (Spiro-USB100; Medical Electronic Construction, Brussels, Belgium). The patients were asked to produce the vowel/a/three times at a distance of 30 cm from the microphone in a sound-treated room. We used MDVP® software (KayPentax®, NJ, USA) to measure the most frequently used acoustic parameters, including mean fundamental frequency (MF0), standard deviation of F0 (STD), fundamental frequency variation (vF0), jitter percent (Jitt), relative average perturbation (RAP), pitch perturbation quotient (PPQ), smoothed pitch perturbation quotient (sPPQ), phonatory fundamental frequency range (PFR), shimmer percent (Shim), amplitude perturbation quotient (APQ), smoothed amplitude perturbation quotient (sAPQ), peak-to-peak amplitude variation (vAm) and noise harmonic ratio (NHR). The acoustic parameters were determined for the entire signal of the three sustained vowel productions (with the exclusion of the first and the last second because of their instability). Moreover, we conducted a correlation analysis to study the relationships among RSI, RFS, adherence to the recommended diet and objective voice quality measurements.

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS v22.0; IBM Corp., NY, USA). Changes in RSI, RFS, and aerodynamic and acoustic measurements were analysed 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.

3 | RESULTS

From the 122 patients, 80 completed the study and 42 were excluded for many reasons (ie aerodigestive tract infections during the last month before the post-treatment consultation; absence to the medical appointment 3 months after the treatment initiation; stopping of treatment during the treatment period; diagnosis of a Parkinson disease during the treatment time; intake of neuroleptics during the last month). Eighty patients were followed up for 3 months, and 41 completed the 6-month follow-up (Figure 1). The epidemiological and clinical characteristics of the included patients are described in Table 1. Of the 41 patients who completed the study, eight were non-responders after 6 months of treatment. The diagnosis was confirmed in these patients with pH/impedance monitoring.

The mean RSI and RFS values were 22.03 ± 6.78 and 10.65 ± 2.38, respectively, at baseline, and they significantly decreased to 8.93 ± 6.13 and 4.88 ± 3.16 at 3 months, respectively, after which no further significant improvement was found (Table 2). After the first 3 months of treatment, all individual RSI and RFS items (excepted subglottic oedema) showed significant improvement. Some clinical images of signs of LPR are available before and after treatment in Figure 2. From 3-6 months of treatment, we only found significant improvement of the mean values for globus sensation and posterior commissure hypertrophy (Table 2), which were significantly correlated ($P = .006$; Spearman's correlation test).

Concerning adherence to the diet regimen, we found mean scores of 6.42 ± 1.80 (3 months) and 6.86 ± 1.42 (6 months). Our statistical analysis found significant negative correlations between adherence to diet and the RSI score 3 months after treatment ($P = .001$; Spearman's correlation test). In addition, the mean score of diet adherence was negatively correlated with the pyrosis score at 3 ($P = .008$) and 6-month ($P = .016$) post-treatment.

From the blinded evaluations of perceptual voice quality, we found significant improvements in the mean grades for dysphonia ($P = .005$), roughness ($P = .002$), strain ($P = .013$), and instability ($P = .012$) after the first 3 months of treatment (Table 3). The mean GRBASI values did not change significantly from 3 to 6 months. The mean values for MPT and PQ were 15.01 ± 7.63 and 275.53 ± 120.30, respectively, at pre-treatment and 16.51 ± 7.54 and 250.37 ± 97.50, respectively, at 3 months post-treatment, which was significantly different ($P < .034$); however, these values did not improve from 3 to 6 months post-treatment (Table 4). Changes in acoustic measurements during the empirical treatment are described in Table 4. The most important acoustic improvements

TABLE 1 Clinical characteristics of patients

	Male (N = 40)	Female (N = 40)	Total	%
Mean age (y)	55	47.6	51.3	–
BMI (kg/m2)	27.57	25.21	26.36	–
Side effects	0	0	0	0
Main complaints				
Globus sensation	9	7	16	20
Dysphonia	5	11	16	20
Cough	5	6	11	13.75
Odynophagia	5	4	9	11.25
Heartburn	2	5	7	8.75
Post-nasal drip/Sticky mucus	1	6	7	9
Throat clearing	2	4	6	7.5
Dysphagia	3	2	5	6.25
Otalgia	0	1	1	1.25
Dyspepsia	1	0	1	1.25
Breathing difficulties	1	0	1	1.25
Symptoms (RSI)				
Throat clearing	38	32	70	88
Dysphonia	35	32	67	84
Heartburn	33	33	66	83
Post-nasal drip/Sticky mucus	32	30	62	78
Cough	31	31	62	78
Globus sensation	30	29	59	74
Cough after eating/lying down	23	24	47	59
Breathing difficulties	17	26	43	54
Dysphagia	18	23	41	51

The entire cohort was composed of 80 LPR patients.
BMI, body mass index; LPR, laryngopharyngeal reflux; y, years.

TABLE 2 Symptoms and signs during treatment in LPR patients

	Clinically diagnosed LPR patients				
Scales	Pre-treatment	3-month N = 80	6-month N = 41	p-value pre-treatment vs 3-month*	p-value 3-month vs 6-month*
RSI	22.03 ± 6.78	8.93 ± 6.13	6.57 ± 5.72	<.001	.062
Voice problem	2.71 ± 1.71	1.29 ± 1.28	0.97 ± 1.09	<.001	.939
Throat clearing	3.63 ± 1.72	1.78 ± 1.48	1.49 ± 1.46	<.001	.733
Post-nasal drip	2.73 ± 1.88	1.25 ± 1.45	0.95 ± 1.29	<.001	.271
Dysphagia	1.35 ± 1.62	0.46 ± 1.04	0.22 ± 0.58	<.001	.072
Coughing post-eating & lying down	1.95 ± 1.97	0.65 ± 1.21	0.51 ± 1.12	<.001	.913
Breathing difficulties	1.54 ± 1.71	0.62 ± 1.16	0.43 ± 0.87	<.001	.794
Troublesome cough	2.44 ± 1.88	0.73 ± 1.07	0.32 ± 0.63	<.001	.191
Globus pharyngeus	2.65 ± 1.93	1.06 ± 1.46	0.59 ± 1.26	<.001	**.019**
Pyrosis, heartburn & chest pain	3.06 ± 1.84	1.05 ± 1.40	1.05 ± 1.20	<.001	.803
RFS	10.65 ± 2.38	4.88 ± 3.16	3.89 ± 2.64	<.001	.179
Subglottic oedema	0.06 ± 0.33	0.01 ± 0.01	0.00 ± 0.00	.102	1.00
Ventricular obliteration	1.10 ± 1.42	0.56 ± 1.11	0.32 ± 0.75	.001	.130
Arytenoid/diffuse redness	3.05 ± 1.05	1.44 ± 1.20	1.19 ± 0.99	<.001	.196
Vocal folds oedema	1.26 ± 0.79	0.39 ± 0.56	0.27 ± 0.56	<.001	.071
Diffuse laryngeal oedema	1.16 ± 0.97	0.47 ± 0.73	0.22 ± 0.48	<.001	.143
Posterior commissure hypertrophy	2.13 ± 0.68	1.18 ± 0.83	1.08 ± 0.86	<.001	**.012**
Granuloma/Granulation	0.56 ± 0.90	0.28 ± 0.70	0.32 ± 0.75	.011	.317
Endolaryngeal mucous	1.33 ± 0.95	0.56 ± 0.90	0.49 ± 0.87	<.001	.808

RSI is a self-administered questionnaire completed by each subject at every visit. Each of the items is related to LPR and is scored from 0 (no problem) to 5 (severe problem). The total score is found by adding all items' scores (/45). RFS is a score of LPR signs. RFS ranges from a lowest possible score of 0 (normal larynx) to a worst possible score of 26.

LPR, laryngopharyngeal reflux; RFS, reflux finding score; RSI, reflux symptom index.

Wilcoxon signed-rank test.

after 3 months of treatment were found for the intensity short-term (Shim, APQ, and sAPQ) and mid-term (vAm) and frequency short-term (Jitt, RAP, and PPQ) and mid-term (PFR) perturbation parameters. No acoustic parameters improved from 3 to 6 months post-treatment.

Changes in the RSI, RFS and voice quality measurements along the pantoprazole treatment course are described in Figure 3. Overall, we found a similar pattern in the evolution of RSI, RFS, and Jitt values throughout the empirical treatment. PQ and Shim had similar patterns of evolution that were not exactly similar to those of RSI, RFS and Jitt.

The study of signs (RFS) and objective voice quality assessments revealed significant correlations among Shim, NHR values and the granulation score (Table 5). A correlation analysis for clinical characteristics, RSI, and RFS showed a negative correlation between the pyrosis sensation score and the patient's age ($P = .003$). Moreover, as shown in Figure 3, the scores for globus sensation and posterior commissure hypertrophy were strongly correlated throughout the treatment course ($P = .006$; Spearman's correlation test). We did not find a correlation between the RSI and RFS total scores or between vocal fold oedema and objective voice quality assessments.

4 | DISCUSSION

The causal relationship between LPR and laryngeal disorders was originally identified at the end of the 1960s by Cherry and Marguelies.[19] Since that time, many case-controlled studies have supported the association between LPR and chronic laryngitis, hoarseness, and the development of benign laryngeal lesions.[11,16,20-22] Prospectively, the real impact of empirical treatment on voice quality remains unclear yielding some controversial conclusions regarding the usefulness of voice quality as treatment outcome.[12]

To improve the management of LPR patients, Belafsky et al developed RSI and RFS, two reliable scales that are widely used for LPR diagnosis and follow-up throughout the world.[16] Many studies found that total scores of RSI and RFS improved from baseline to 3 or 6 months post-treatment,[3,13,16] but a few trials were really interested in the evolution of individual symptoms and signs along the empirical therapeutic course. Moreover, we often see in our clinical practice that many patients need over 3 months of treatment to completely be cured. In this study, we mainly found that most of signs and symptoms significantly improved from baseline to 6 months post-treatment with different patterns. Thus, some complaints and signs, especially globus sensation and posterior

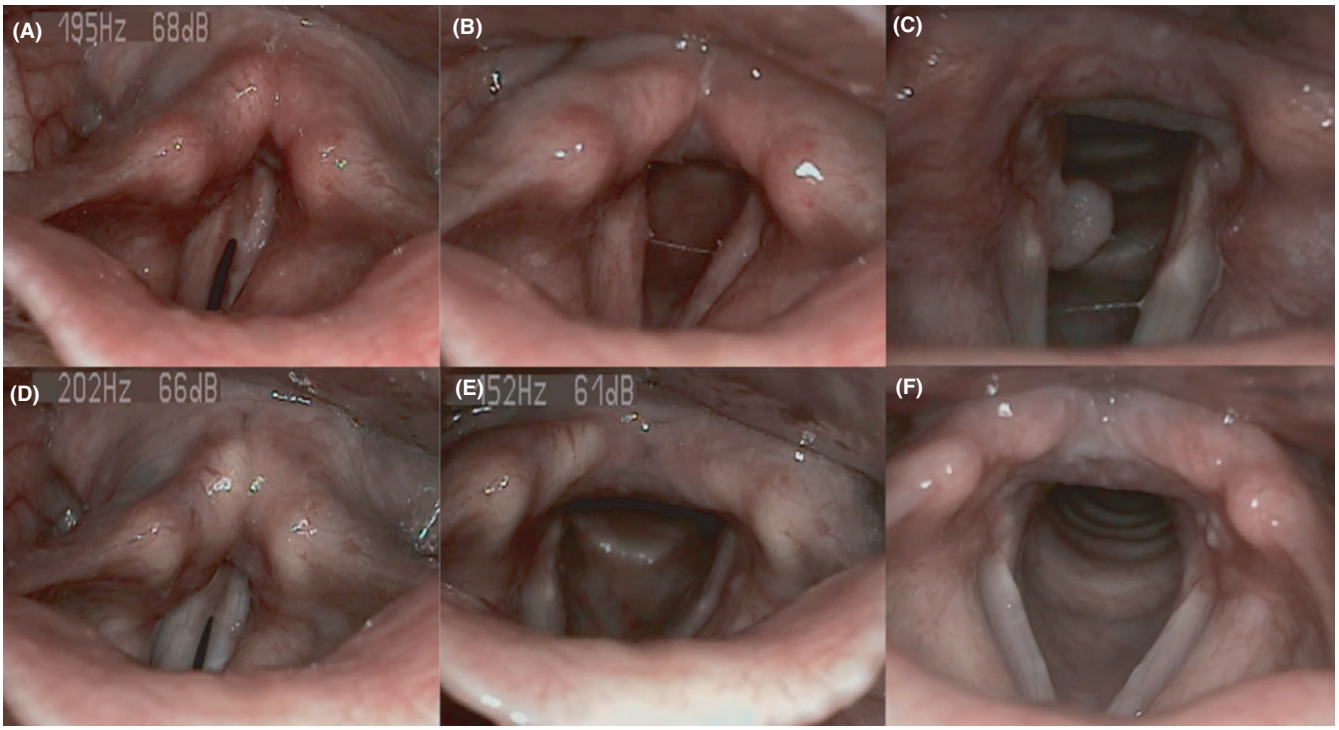

FIGURE 2 Typical signs observed before vs after treatment in LPR patients. Pre-treatment laryngoscopic signs (A, B, C) suggesting laryngopharyngeal reflux (posterior commissure hypertrophy, laryngeal and inter-arytenoid redness, granuloma, and vocal folds irritation). Post-treatment laryngoscopic signs (D, E, F) showing an improvement of the laryngoscopic signs

TABLE 3 Perceptual voice quality during treatment in LPR patients

	Clinically diagnosed LPR patients				
Scales	Pre-treatment	3-month	6-month	P-value pre-treatment vs 3-month	P-value 3-month vs 6-month
Grade	0.94 ± 0.81	0.57 ± 0.71	0.33 ± 0.52	**0.005**	1.00
Roughness	0.85 ± 0.76	0.51 ± 0.66	0.50 ± 0.55	**0.002**	0.157
Breathing	0.29 ± 0.52	0.29 ± 0.58	0.33 ± 0.52	0.985	0.564
Asthenia	0.25 ± 0.50	0.31 ± 0.53	0.17 ± 0.41	0.346	0.317
Strain	0.72 ± 0.74	0.48 ± 0.62	0.17 ± 0.40	**0.013**	0.564
Instability	0.69 ± 0.71	0.40 ± 0.58	0.30 ± 0.50	**0.012**	0.157

LPR, laryngopharyngeal reflux.
Wilcoxon signed-rank test.

commissure hypertrophy, need more time to improve compared to other, supporting a benefit of continued but titrated PPIs from 3 to 6 months in patients with these findings.

Concerning the treatment, we identified a significant impact of adherence to the treatment regimen on the RSI improvement but not on the RFS improvement. This positive correlation was strongest for pyrosis sensation after 6 months of treatment. As it has long been known that diet represents an important component of the treatment's efficiency, our observations could suggest the occurrence of a 'suggestive effect' for patients who adhered to the regimen because they perceived better improvement of their main symptoms.[18] Indeed, the effect of suggestion can be defined as the psychological process by which one person guides the feelings, thoughts, or behaviour of another person. Regarding the lack of improvement of signs related to LPR, we might postulate that patients who well respected diet (respecting our initial advices) experienced better improvement of symptoms (RSI) with regard to the initial explanation about the importance of diet. Another explanation could involve the lack of consideration of many signs related to LPR in RFS (ie oro- and hypopharyngeal erythema, oedema, laryngeal keratosis, tongue tonsil hypertrophy, coated tongue, etc.) as objective therapeutic outcomes. Thus, the lack of consideration of some signs usually found in LPR can bias the real impact of diet on signs related to LPR. The existence of a placebo effect in LPR treatment has long been suggested but not completely understood.[9,23] Our observations could enrich the disparate knowledge on the subject with a potential

TABLE 4 Objective voice quality measurements during treatment in LPR patients

		Clinically diagnosed LPR patients				
Acoustic & aerodynamic	U	Pre-treatment	3-month N = 80	6-month N = 41	P-value pre-treatment vs 3-month	P-value 3-month vs 6-month
MPT	s	15.01 ± 7.63	16.51 ± 7.54	16.93 ± 6.52	**0.021**	0.265
PQ	mL/s	275.53 ± 120.30	250.37 ± 97.50	242.92 ± 95.95	**0.034**	0.481
Fundamental frequency						
MF0	Hz	155.14 ± 45.52	154.22 ± 42.11	151.87 ± 38.60	0.674	0.596
F0 short-term perturbation cues						
Jitt	%	2.63 ± 1.50	2.39 ± 2.22	2.06 ± 1.13	**0.004**	0.295
RAP	%	1.56 ± 0.89	1.42 ± 1.29	1.22 ± 0.66	**0.004**	0.302
PPQ	%	1.59 ± 0.95	1.46 ± 1.52	1.24 ± 0.72	**0.004**	0.410
sPPQ	%	2.45 ± 1.92	2.31 ± 2.55	1.79 ± 1.14	0.104	0.395
F0 mid-term perturbation cues						
PFR		5.33 ± 2.92	4.71 ± 2.72	4.41 ± 2.05	**0.036**	0.878
STD	Hz	7.51 ± 7.49	6.70 ± 9.21	5.00 ± 3.96	0.113	0.270
vF0	%	4.54 ± 3.94	4.05 ± 4.30	3.23 ± 3.34	0.606	0.329
Intensity short-term perturbation cues						
Shim	%	7.17 ± 2.98	6.63 ± 3.36	6.91 ± 3.24	**0.012**	0.418
APQ	%	5.65 ± 2.64	5.23 ± 2.66	5.45 ± 2.52	**0.018**	0.503
sAPQ	%	9.77 ± 3.12	8.75 ± 2.89	8.69 ± 2.80	**0.007**	0.911
Intensity mid-term perturbation cues						
vAm	%	16.35 ± 4.80	14.59 ± 4.88	14.42 ± 3.57	**0.001**	0.922
Noise-related measurements						
NHR		0.19 ± 0.06	0.18 ± 0.09	0.53 ± 2.23	0.170	0.706

s, second; dB, decibels; Hz, Hertz; LPR, laryngopharyngeal reflux; MPT, maximum phonation time; mL/s, millilitre/second; PQ, phonatory quotient. Wilcoxon signed-rank test.

'suggestive effect' as a concurrent hypothesis. Concerning the association between the elderly and the low rate of pyrosis complaints, we attributed this observation to the unusual clinical presentation related to ageing following the degeneration of the neurologic system.[24]

Many studies that have examined voice quality as a treatment outcome in LPR diseases have reported controversial results.[11,12,14,15] Overall, our study reports significant improvements of grade of dysphonia, and Jitt from baseline to 6 months. Perceptually, we observed a significant improvement in the grades of dysphonia from baseline to 6 months post-treatment. Our results are consistent with those of Park et al[25], who found significant improvement of the blinded evaluation of the grade of dysphonia after 3 months of PPIs therapy. We observed that the overall evolution of grade of dysphonia has the same pattern as the evolution of some clinical or acoustic evaluations, such as RSI, RFS, or jitter, confirming for the latter, the potential relationships between perceptual judgment and objective measurements of voice quality.[26] Our study identified significant improvements in both aerodynamic (PQ) and acoustic (ie, Jitt, and Shim) measurements after 3 months of treatment and Jitt from baseline to 6 months of treatment. These findings supported the observations of Jin et al and Shaw et al, who found improvements in both percent jitter and percent shimmer 3 months post-therapy.[3,11] However, our acoustic comparison with the current literature has to be treated with caution because of inconsistencies between studies in the methods used to measure acoustic parameters. Indeed, it has been demonstrated that the potential effect of the treatment on acoustic parameters may or may not be statistically demonstrated depending on the time interval over which the acoustic parameters are measured.[12,27] For this reason, that we measured acoustic cues for the entire signal of the three sustained vowel productions and not only the middle or a segment of the signal.

As observed in the evolution of RSI, RFS, and perceptual voice quality assessments, from 3 to 6 months of treatment, we did not find significant evolution of acoustic or aerodynamic measures in LPR patients. In other words, voice results remained stable from 3 to 6 months. No previous study has examined voice quality changes after 3 months of treatment, which limits our literature comparisons. The lack of improvement of voice quality and the specified clinical improvement (ie globus and posterior commissure hypertrophy) from 3 to 6 months support the current cost-effective therapeutic scheme consisting of an initial treatment of 3 months with titration for the 3 additional months.

As previously reported,[7,12,26] current debate exists concerning the relationship between clinical and voice quality improvements in

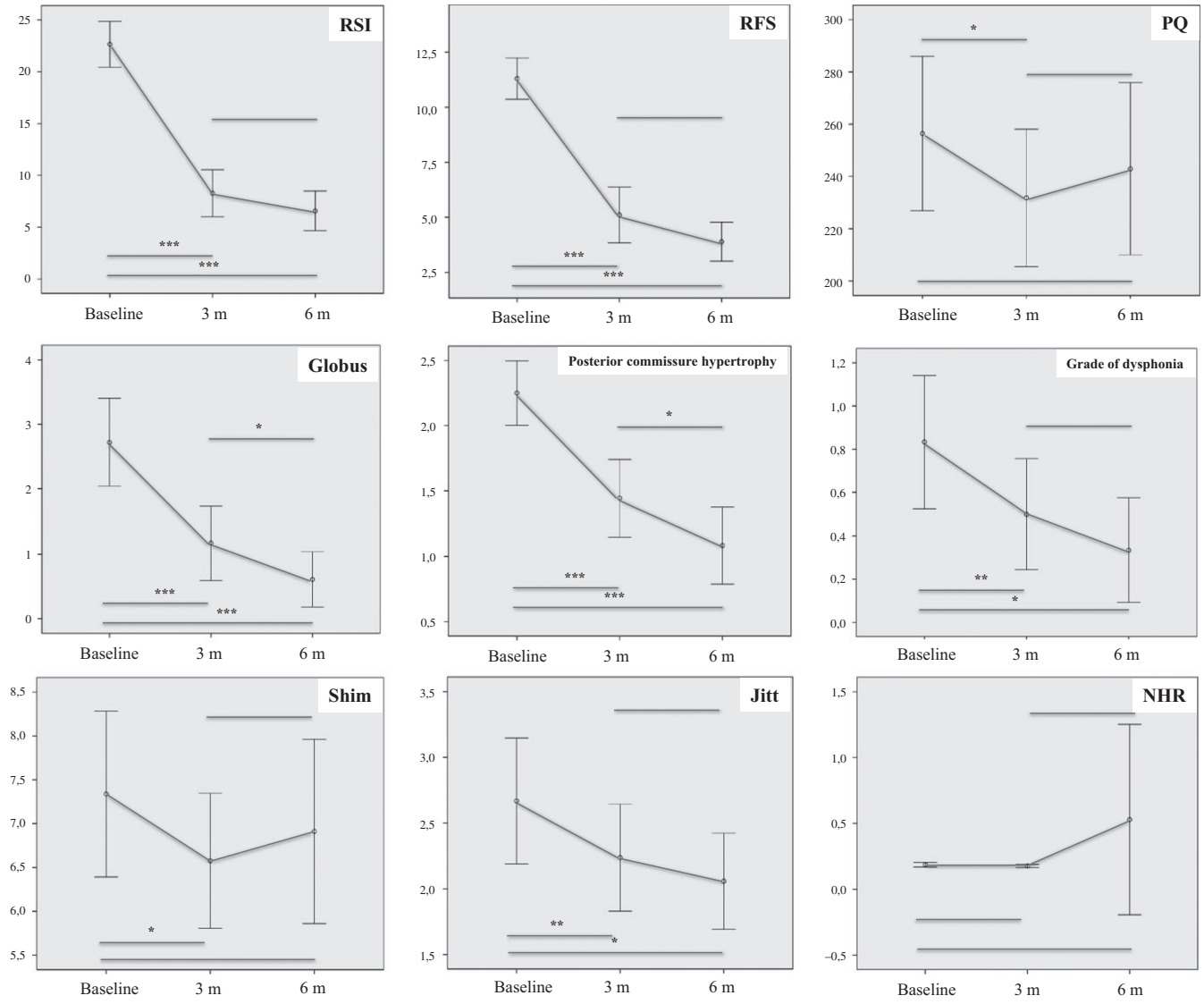

FIGURE 3 Evolution of RSI, RFS, globus sensation, posterior commissure hypertrophy and some pertinent voice quality assessments during the treatment in LPR patients. Jitt = percent jitter; LPR = laryngopharyngeal reflux; m = month; NHR = noise-to-harmonic ratio; PQ = phonatory quotient; RFS = reflux finding score; RSI = reflux symptom index; Shim = percent shimmer. Statistical significances are expressed by p-value according to the Wilcoxon rank test (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$)

LPR patients. In this study, we also observed a similar pattern of evolution of Shim and PQ values that may be explained by the relationship between Shim values and PQ. Thus, Shim assesses the short-term instability of voice intensity that closely depends on the subglottic airflow, which is indirectly measured by the phonatory quotient.[28] In other words, instability or a deterioration of PQ could be more strongly associated with an increase in the Shim values. Our results also exhibited that the evolution of NHR from 3 to 6 months differed from the evolution of jitter, shimmer, RSI and RFS. This unexpected evolution particularly supports that NHR measurement is less representative of the clinical evolution throughout the empirical treatment and less useful as therapeutic outcome. However, Hamdan et al found similar findings about the NHR evolution along the treatment in comparison with other acoustic measurements.[14] In a general way, the similar evolution of RSI, RFS, jitter and perceptual voice strengthens the interest of these evaluations as LPR therapeutic outcome.

Finally, to study the pathophysiological mechanisms underlying the voice quality alterations related to LPR, we conducted correlation analysis among videolaryngostroboscopic signs and acoustic measurements. First, as found in another study,[3] we did not identify a relationship between vocal fold oedema and any acoustic measurements, contradicting the notion that vocal fold oedema is the causative factor of irregular vocal fold vibrations leading to hoarseness. As described in a recent pathophysiological review, other findings could explain the development of hoarseness related to LPR. Indeed, the occurrence of microtraumatism, thickening, ulcerations and keratosis of the margin of the vocal folds, and inflammatory modifications of the Reinke space could modify the vocal folds' biomechanical properties resulting in hoarseness.[20] In the present study, we did not

TABLE 5 Correlation analysis (p-values) between signs and main acoustic measurements in LPR patients

Clinically diagnosed LPR patients			
	Acoustic measurements		
	Jitt	Shim	NHR
RFS	0.818	0.953	0.598
Subglottic oedema	0.661	0.461	0.764
Ventricular obliteration	0.800	0.459	0.719
Arytenoid/diffuse redness	0.806	0.250	0.179
Vocal folds oedema	0.440	0.293	0.326
Diffuse laryngeal oedema	0.375	0.449	0.120
Posterior commissure hypertrophy	0.488	0.473	0.055
Granuloma/Granulation	0.763	**0.031**	**0.042**
Endolaryngeal mucous	0.832	0.956	0.888

HNR, harmonic-to-noise ration; Jitt, Jitter; LPR, laryngopharyngeal reflux; RFS, reflux finding score; Shim, Shimmer.

evaluate these signs regarding our choice to use RFS as sign's instrument. It is important to specify that most of these clinical findings are not described in the standardised clinical instruments available in the literature such as RFS; limiting the study of laryngeal signs involved in the development of hoarseness related to LPR. This study highlights that, at the exception of globus and posterior commissure hypertrophy, LPR symptoms, signs, and voice quality only significantly improved throughout the three-first months of treatment. Voice quality improvement seems to be consistently associated with clinical improvement, especially jitter measurement. In this context, our results suggest that voice quality measurements can be used as indicators of the empirical treatment outcomes in clinically suspected LPR patients.

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CONFLICT OF INTEREST

The authors have no conflict of interest

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REFERENCES

1. Koufman JA, Aviv JE, Casiano RR, et al. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg*. 2002;127:32-35.
2. Sen P, Georgalas C, Bhattacharyya AK. A systematic review of the role of proton pump inhibitors for symptoms of laryngopharyngeal reflux. *Clin Otolaryngol*. 2006;31:20-24; discussion 24.
3. Jin BJ, Lee YS, Jeong SW, et al. Change of acoustic parameters before and after treatment in laryngopharyngeal reflux patients. *Laryngoscope*. 2008;118:938-941.
4. Poelmans J, Feenstra L, Tack J. Determinants of long-term outcome of patients with reflux-related ear, nose, and throat symptoms. *Dig Dis Sci*. 2006;51:282-288.
5. Lee YS, Choi SH, Son YI, et al. Prospective, observational study using rabeprazole in 455 patients with laryngopharyngeal reflux disease. *Eur Arch Otorhinolaryngol*. 2011;268:863-869.
6. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991;101(4 Pt 2 Suppl 53):1-78.
7. Sataloff RT, Hawkshaw MJ, Gupta R. Laryngopharyngeal reflux and voice disorders: an overview on disease mechanisms, treatments, and research advances. *Discov Med*. 2010;10:213-224.
8. Noordzij JP, Khidr A, Desper E, et al. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. *Laryngoscope*. 2002;112:2192-2195.
9. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA*. 2005;294:1534-1540.
10. Gupta N, Green RW, Megwalu UC. Evaluation of a laryngopharyngeal reflux management protocol. *Am J Otolaryngol*. 2016;37:245-250.
11. Shaw GY, Searl JP. Laryngeal manifestations of gastroesophageal reflux before and after treatment with omeprazole. *South Med J*. 1997;90:1115-1122.
12. Lechien JR, Finck C, Costa de Araujo P, et al. Voice outcomes of laryngopharyngeal reflux treatment: a systematic review of 1483 patients. *Eur Arch Otorhinolaryngol*. 2016;23:1-23.
13. Lechien JR, Huet K, Khalife M, et al. Impact of laryngopharyngeal reflux on subjective and objective voice assessments: a prospective study. *J Otolaryngol Head Neck Surg*. 2016;45:59.
14. Hamdan AL, Sharara AI, Younes A, et al. Effect of aggressive therapy on laryngeal symptoms and voice characteristics in patients with gastroesophageal reflux. *Acta Otolaryngol*. 2001;121:868-872.
15. Selby JC, Gilbert HR, Lerman JW. Perceptual and acoustic evaluation of individuals with laryngopharyngeal reflux pre- and post-treatment. *J Voice*. 2003;17:557-570.
16. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope*. 2001;111:1313-1317.
17. Wan Y, Yan Y, Ma F, et al. LPR: how different diagnostic tools shape the outcomes of treatment. *J Voice*. 2014;28:362-368.
18. Koufman JA. Low-acid diet for recalcitrant laryngopharyngeal reflux: therapeutic benefits and their implications. *Ann Otol Rhinol Laryngol*. 2011;120:281-287.
19. Cherry J, Margulies SI. Contact ulcer of the larynx. *Laryngoscope*. 1968;78:1937-1940.
20. Lechien JR, Saussez S, Harmegnies B, et al. Laryngopharyngeal reflux and voice disorders: a multifactorial model of etiology and pathophysiology. *J Voice*. 2017;31:733-752.
21. Kumar R, Bhat JS. Aerodynamic analysis of voice in persons with laryngopharyngeal reflux. *Online J Health Allied Scs*. 2008;7:5.
22. Ross JA, Noordzji JP, Woo P. Voice disorders in patients with suspected laryngo-pharyngeal reflux disease. *J Voice*. 1998;12:84-88.
23. Sereg-Bahar M, Jansa R, Hocevar-Boltezar I. Voice disorders and gastroesophageal reflux. *Logoped Phoniatr Vocol*. 2005;30:120-124.
24. Lechien JR, Finck C, Huet K, et al. Impact of age on laryngopharyngeal reflux disease presentation: a multi-center prospective study. *Eur Arch Otorhinolaryngol*. 2017;274:3687-3696.

25. Park JO, Shim MR, Hwang YS, et al. Combination of voice therapy and antireflux therapy rapidly recovers voice-related symptoms in laryngopharyngeal reflux patients. *Otolaryngol Head Neck Surg*. 2012;146:92-97.
26. Millet B, Dejonckere PH. What determines the differences in perceptual rating of dysphonia between experienced raters? *Folia Phoniatr Logop*. 1998;50:305-310.
27. Lechien JR, Delvaux V, Huet K, et al. Phonetic approaches of laryngopharyngeal reflux disease: a prospective study. *J Voice*. 2017;31:119.e11-119.e20.
28. Yu P, Ouaknine M, Revis J, et al. Objective voice analysis for dysphonic patients: a multiparametric protocol including acoustic and aerodynamic measurements. *J Voice*. 2001;15:529-542.

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