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LARYNGOLOGY

Acoustic measurements are useful therapeutic indicators of patients with dysphonia-related to reflux

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Abstract

Objectives The objective is to study the usefulness of acoustic measurements as therapeutic outcomes for patients with dysphonia related to laryngopharyngeal reflux (LPR).

Methods From September 2019 to April 2021, 120 patients with LPR at the hypopharyngeal-esophageal multichannel intraluminal impedance pH-monitoring (HEMII-pH) were prospectively recruited from three University Hospitals. They were divided in two groups regarding the presence of dysphonia. The treatment consisted of a combination of diet, proton-pump inhibitors, magaldrate and alginate for 3–6 months. The following clinical and acoustic evaluations were studied regarding groups at baseline, 3- and 6-month posttreatment: reflux symptom score (RSS), reflux sign assessment (RSA), percent jitter, percent shimmer and noise-to-harmonic ratio (NHR).

Results A total of 109 patients completed the evaluations, accounting for 49 dysphonic and 60 non-dysphonic individuals. HEMII-pH, gastrointestinal endoscopy, baseline clinical and acoustic features were comparable between groups. RSS and RSA significantly improved from pre- to 3-month posttreatment in both groups. Jitter, Shimmer and NHR significantly improved from pre- to 3-month posttreatment in dysphonic patients, without additional 3- to 6-month posttreatment changes. Acoustic parameters did not change throughout treatment in patients without dysphonia.

Conclusion Acoustic measurements may be an interesting indicator of treatment in LPR patients who reported dysphonia. In this group of individuals, the evolution of acoustic parameters was consistent with the evolution of symptoms and findings.

Keywords Reflux · Laryngopharyngeal · Gastroesophageal · Voice · Acoustic · Dysphonia · Impedance · pH monitoring

Introduction

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to direct and indirect effect of gastroduodenal content reflux, which induces morphological changes in the upper aerodigestive tract [1]. Symptoms are non-specific and include globus sensation, throat clearing, pharyngeal sticky mucus, dysphonia and throat pain [1]. Dysphonia is one of the most frequent symptoms, accounting for up to 55% of LPR patients [1, 2]. Dysphonia may be attributed to pepsin-related injuries, macroscopic and microscopic histological changes on the vocal folds, which may lead to aerodynamic and acoustic measurement impairments [3–5]. Because evolutions of non-specific symptoms and findings are still subjective, the identification of objective indicators of the treatment effectiveness remains challenging [1]. According to the high prevalence of LPR-related dysphonia, many authors investigated the

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usefulness of acoustic measurements as objective therapeutic outcomes [3, 6–8]. Acoustic parameters appeared better in healthy controls compared with LPR patients but it is still controversial whether acoustic measurements improve while treating LPR [6–8].

In this study, we investigated acoustic measurements throughout 3- to 6-month antireflux therapy according to the presence of dysphonia in patients. Precisely, we sought to determine whether acoustic measurements may be useful as indicators of treatment for patients with laryngopharyngeal reflux (LPR) and self-reported dysphonia.

Methods

Ethical considerations

Patients had to consent to participate to the study (IRB-CHU Saint-Pierre, Brussels, n°BE076201837630).

Patients with LPR symptoms (i.e. globus sensation, throat clearing, dysphagia, cough, dysphonia) were prospectively recruited from three University European hospitals (Foch Hospital, Paris, France; Cesar de Pape Hospital and CHU Saint-Pierre, Brussels, Belgium). Patients were categorized in two groups according to their initial symptoms: patients with self-reported dysphonia and those without self-reported dysphonia. In practice, the majority of dysphonic patients consulted in our laryngology & swallowing units, while others consulted in our general otolaryngological department.

To be included, all patients had to have a positive LPR diagnosis at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH study, consisting of the presence of ≥ 1 hypopharyngeal reflux events [9]. Gastrointestinal (GI) endoscopy was proposed to elderly (> 55 year) or those with GI symptoms. Patients with the following outcomes were excluded: active smoker, alcoholic (> 3 glasses/day), patients with an history of upper respiratory tract infection within the last month, neurological or psychiatric illness, head and neck malignancy, head and neck radiotherapy, inhaled corticosteroid intake, active seasonal allergies, asthma or history of phonosurgery or vocal fold lesion.

Hypopharyngeal–esophageal multichannel intraluminal impedance-pH testing

The HEMII-pH catheter placement and composition were reported in previous studies [10], and respect some recent recommendations [11]. The probe was composed of eight impedance ring pairs and two pH electrodes (Versaflex Z®, LPR ZNID22 + 8R FGS 9000–17; Digitrapper pH-Z testing System, Medtronic, Hauts-de-France, France). The catheter was introduced transnasally. Six impedance segments were placed along the esophagus zones (Z1–Z6) below the upper esophagus sphincter (UES), while two additional impedance segments were placed 1 and 2 cm above the UES in the pharyngeal cavity. The pH electrodes were placed 2–5 cm above LES and 1–2 cm above UES, respectively. The examination started in the morning at rest (8:00 AM) and lasted 24 h.

Pharyngeal reflux event was defined as an episode that reached two hypopharyngeal impedance sensors. LPR diagnosis consisted of ≥ 1 acid or nonacid pharyngeal reflux event. Acid reflux event was defined as an episode with $pH \leq 4.0$. Nonacid reflux consisted of a pharyngeal reflux event with $pH > 4.0$. The HEMII-pH tracing was electronically analyzed by the software and the result was verified by two senior physicians. Acid LPR was defined when the ratio of number of acid pharyngeal events/number of nonacid events was > 2. LPR was defined as nonacid or alkaline when the ratio of number of acid events/number of nonacid events < 0.5. Mixed or weakly acid reflux consisted of a ratio ranged from 0.51 to 2.0. GERD diagnosis was based on Lyon guidelines [12].

Treatment

All patients were instructed to respect a validated European diet based on the consumption of high-protein, low-fat, alkaline, plant-based foods and beverages [13]. In addition, HEMII-pH findings were used to determine the personalized drug-based treatment [10]. The first line was based on a combination of proton pump inhibitors (PPIs, Pantoprazole), post-meal alginate (Gaviscon Advance®, Reckitt Benckiser, Slough, UK) or magaldrate (Riopan®, Takeda, Zaventem, Belgium) for 3 months. Patients with acid LPR were treated with pantoprazole and post-meal alginate. The treatment of nonacid LPR patients consisted of post-meal magaldrate or alginate, whereas individuals with weakly acid LPR received a combination of pantoprazole and post-meal alginate or magaldrate if there was no satisfactory response with alginate. Patients with nighttime reflux at the HEMII-pH tracing received additional alginate or magaldrate (alkaline LPR) at bedtime. Patient adherences to diet and medication were assessed through a ten-point Likert scale, ranging from 0 (= no respect) to 10 (= perfect respect).

A RSS reduction of < 20% or a worsening of RSS were defined as an uncertain therapeutic response. A RSS reduction of 20–39.99% was defined as a mild therapeutic response. A RSS reduction of 40–59.99% was considered as a moderate therapeutic response. The treatment was titrated for patients with mild and moderate therapeutic response. A RSS reduction of 60–79.9% was defined as high therapeutic response. The response of patients with a RSS reduction of $\geq 80\%$ or a posttreatment RSS ≤ 13 [10] was defined as complete. The treatment was stopped in individuals exhibited high or complete response, while it was adjusted in patients with mild-to-moderate (decrease drugs and doses)

or poor (drug changes) response. The therapeutic response was evaluated at 6-month posttreatment.

Clinical and voice quality evaluations

Symptoms were evaluated with Reflux Symptom Score (RSS) [14]. Findings were rated with Reflux Sign Assessment (RSA) by two laryngologists in a blind manner with videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) [15]. Both raters were chosen because they reported significant interrater reliability ($r_s > 0.600$) [15]. Acoustic measurements were measured on the production of the vowel /a/ two times at a distance of 30 cm from the microphone in a sound-treated room. Acoustic parameters were measured with MDVP® software (KayPentax®, NJ, USA). The following acoustic measurements were considered: jitter percent (Jitt), shimmer percent (Shim) and noise harmonic ratio (NHR). The acoustic parameters were determined for the entire signal of the two sustained vowel productions considering the exclusion of the first and the last second of the vowel because of their instability.

Statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 27.0; IBM Corp, Armonk, NY, USA). The statistical analyses were performed regarding two groups of patients: patients with dysphonia and those without dysphonia. Mann–Whitney *U* and Chi-squared tests were used for the group comparison analyses. The pre- to post-treatment changes were assessed with the Wilcoxon signed-rank test. A level of significance of $p < 0.05$ was used.

Results

One hundred and twenty outpatients were consecutively recruited from September 2019 to April 2021. Among them, 109 patients completed the evaluations, including 49 dysphonic (30 females) and 60 non-dysphonic (29 females) individuals. The chart flow of the study is available in Fig. 1. The epidemiological and clinical findings of both groups are described in Table 1. Groups were comparable regarding age, body mass index, stress level, GI endoscopy, HEMII-pH findings, symptom and sign scores. Dysphonic and non-dysphonic patients reported significant improvements of RSS sub- and total scores from baseline to 3-month posttreatment. RSS did not change from 3- to 6-month posttreatment in both groups (Tables 2 and 3). Similar overall findings were observed for pharyngeal, laryngeal and total RSA scores in both groups, whereas oral sign scores did not change throughout treatment. Note that dysphonic and non-dysphonic patients similarly respected diet (6.78 ± 2.38 vs 6.88 ± 2.34) and medication (7.82 ± 2.22 vs 8.30 ± 1.75) throughout the therapeutic course.

Acoustic analyses reported that jitter, shimmer and NHR significantly improved from baseline to 3-month posttreatment in dysphonic patients (Table 4). There were no further voice changes from 3- to 6-month posttreatment in this group of patients. Acoustic parameters did not change throughout the therapeutic course in patients without dysphonia (Table 5). The multivariate analysis reported significant positive association between NHR values and endolaryngeal mucus scores ($r_s = 0.310$; $p = 0.040$).

The responder rates of dysphonic and non-dysphonic patients are summarized in Table 6. Overall, there was no significant differences in the response to treatment across both groups of patients.

Discussion

The association between reflux and laryngeal disorders was originally identified by Cherry et al. at the end of the 1960s [16]. Since then, many clinical and basic science studies have supported the association between acid LPR, chronic laryngitis and dysphonia, but the usefulness of acoustic parameters as treatment indicators remains unclear [6, 8].

To improve the management of LPR patients, it is usually recommended to use patient-reported outcome questionnaires and finding instruments. It has been supported over the past decades that symptoms and signs of LPR significantly improved from baseline to 3-month posttreatment, while the interest to continue the treatment from 3 to 6 months is still poorly demonstrated and, therefore, controversial [17–19]. In this study, we did not observe significant changes of symptoms and signs from 3 to 6 months of treatment, which was highlighted by the evolution of acoustic measurements. Precisely, we observed that jitter, shimmer and NHR are useful objective indicators of treatment but only in patients who initially complained of dysphonia. The usefulness of acoustic parameters was previously investigated in some prospective studies, where authors focused on patients with suspected LPR [17, 20] or confirmed acid LPR at the HEMII-pH monitoring [6, 21]. In, 2008, Jin et al. observed significant pre- to 3-month posttreatment improvements of jitter, shimmer and HNR in 40 patients with acid LPR at the dual-probe pH monitoring [6]. In the same vein, Wan et al. supported the usefulness of jitter, shimmer and HNR that all improved after 4-week PPI-based therapy in patients with acid LPR at the dual-probe pH study [20]. As in our study, Jin et al. and Wan et al. observed that acoustic parameters reported similar pattern of evolution of both symptoms and findings throughout treatment period [6, 20].

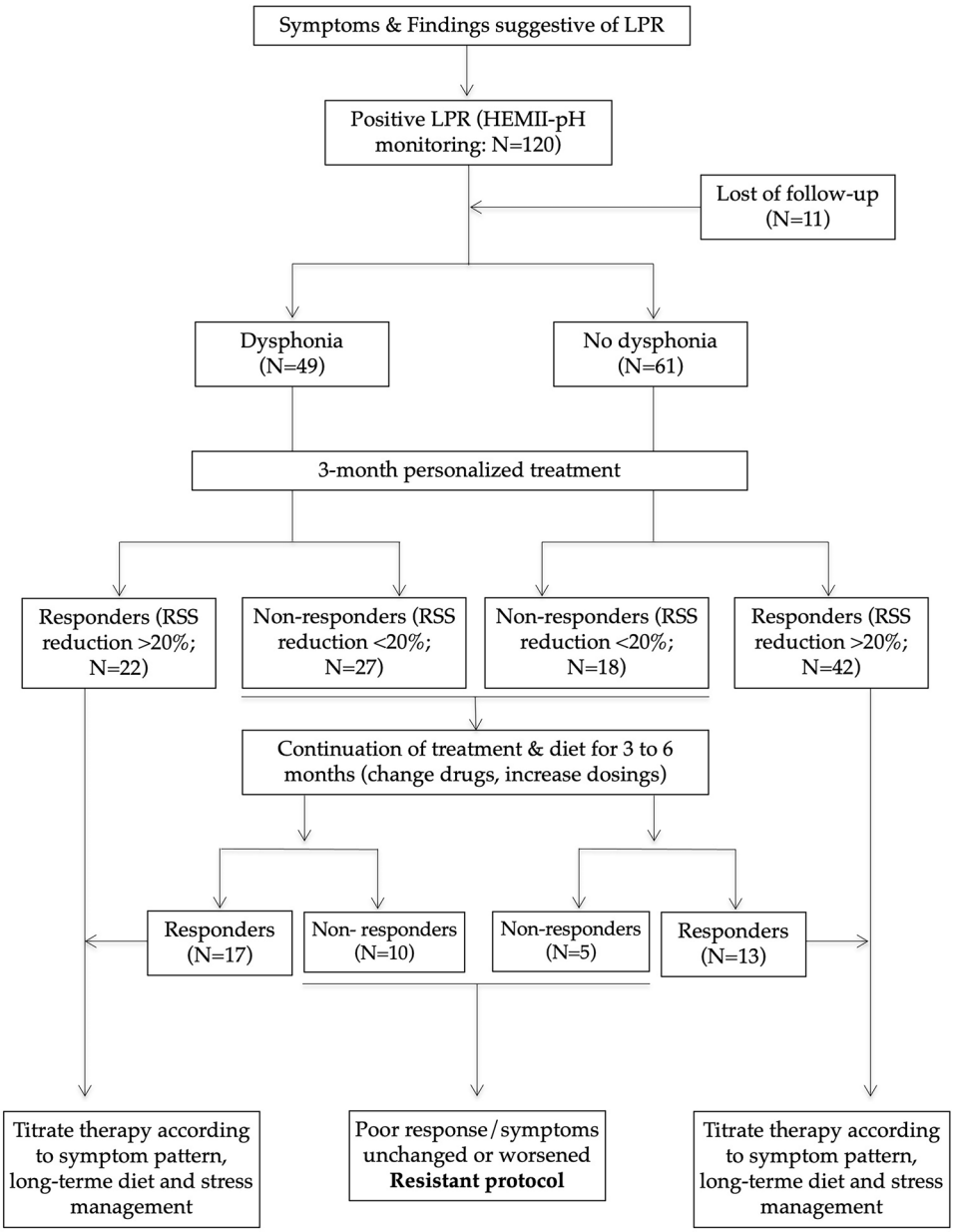

Fig. 1 Chart flow. Medications were titrated in responders. *HEMII-pH* hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring, *LPR* laryngopharyngeal reflux, *RSS* reflux symptom score

To the best of our knowledge, these acoustical studies were the only investigations where patients had a confirmed LPR diagnosis, which limits the comparison with the literature.

In clinical practice, the realization of acoustic analyses is time-consuming and may require some devices and software. In the present study, we sought to determine whether acoustic measurements were useful indicators of treatment in LPR patients with self-reported dysphonia. Our data supported that acoustic measurements may be used more specifically in LPR patients with dysphonia, while they are useless in patients without self-reported dysphonia. This thought appears consistent with the basic science and clinical studies that reported macroscopic and microscopic histological changes on the vocal folds of reflux subjects that are clinically highlighted by acoustic measurements [3–6]. The physiological mechanisms involve the pepsin-related impairments of defense mechanisms of the vocal folds, including mucin production, type III anhydrase carbonic activity, growth factor secretion, which may favor the occurrence of epithelial cell dehiscence, microtraumas, inflammatory infiltrate and macroscopic lesions [3]. Patients with dysphonia had probably more vocal fold impairments and, therefore, they represent a subgroup of LPR patients where the use of acoustic measurements make particularly sense. Future studies are needed to confirm our results while taking care to the method used to measure acoustic parameters. Indeed, it has been demonstrated on reflux patients that depending on the time interval (and the vowel length) over which the acoustic

Table 1 Epidemiological and clinical data of dysphonic and non-dysphonic patients

Characteristics	Dysphonic ($N=49$)	Non-dysphonic ($N=60$)	p value
Age	52.87 ± 18.36	48.00 ± 14.47	NS
Body mass index	26.30 ± 5.56	24.58 ± 4.85	NS
Gender			
Male	19 (38.78)	31 (51.67)	NS
Female	30 (61.22)	29 (48.33)	NS
Level of stress (Likert scale/10)	5.79 ± 2.77	6.87 ± 2.51	NS
Gastrointestinal endoscopy	$N=33$	$N=42$	
Normal	3 (9.09)	5 (11.90)	NS
Esophagitis	17 (51.52)	17 (40.48)	NS
Hiatal hernia	9 (27.27)	16 (38.10)	NS
LES insufficiency	9 (27.27)	17 (40.48)	NS
Gastritis	16 (48.48)	19 (45.24)	NS
Helicobacter pylori	1 (3.03)	5 (11.90)	NS
HEMII-pH feature (m ± SD)			
Pharyngeal acid reflux episodes	13.77 ± 11.22	28.50 ± 16.70	NS
Pharyngeal nonacid reflux episodes	20.65 ± 16.31	9.79 ± 9.73	NS
Total number of pharyngeal reflux episodes	33.43 ± 24.79	37.55 ± 22.68	NS
Pharyngeal reflux episodes upright	27.95 ± 23.12	29.79 ± 20.77	NS
Pharyngeal reflux episodes supine	5.00 ± 6.76	6.45 ± 7.66	NS
Types of reflux			
Acid LPR	22 (44.90)	24 (40.00)	NS
Weakly acid LPR	18 (36.73)	26 (43.33)	NS
Alkaline LPR	9 (18.37)	10 (16.67)	NS
GERD (N)	12 (24.50)	32 (53.33)	
Percentage of time with distal pH < 4	1.88 ± 2.45	10.65 ± 13.43	NS
DeMeester score	7.44 ± 9.36	36.57 ± 41.64	NS
Reflux symptom score	113.56 ± 66.92	120.02 ± 75.87	NS
Reflux sign assessment	25.83 ± 9.86	28.05 ± 8.03	NS

Statistics were performed with Mann–Whitney and Chi-squared tests

GERD gastroesophageal reflux disease, *HEMII-pH* hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing, *LES* lower esophageal sphincter, *LPR* laryngopharyngeal reflux, *NS* non-significant

Table 2 Pre to posttreatment clinical changes in dysphonic patients

Clinical outcomes	Pre-treatment	3 months	p value	6 months	p value
Reflux symptom score					
Otolaryngological score	57.09 ± 34.17	41.86 ± 39.30	0.001	45.69 ± 47.20	NS
Digestive score	35.20 ± 29.98	20.67 ± 38.32	0.001	30.38 ± 40.23	NS
Respiratory score	21.49 ± 24.13	12.77 ± 17.08	0.001	13.97 ± 20.91	NS
RSS—score total	113.56 ± 66.92	75.30 ± 66.20	0.001	90.03 ± 94.04	NS
Reflux sign assessment					
Oral score	4.98 ± 2.84	4.79 ± 2.65	NS	4.48 ± 2.28	NS
Pharyngeal score	9.91 ± 4.91	7.60 ± 3.83	0.001	8.29 ± 4.17	NS
Laryngeal score	11.73 ± 5.94	8.42 ± 4.35	0.001	6.93 ± 5.05	NS
RSA—total score	25.83 ± 9.86	20.72 ± 7.65	0.001	19.54 ± 7.60	NS

NS non-significant, *RSA* reflux sign assessment, *RSS* reflux symptom score

parameters are measured, the clinically demonstrated effect of the medication may or may not be statistically demonstrated [22]. In that way, jitter, shimmer and NHR values may vary regarding the method of measurement.

Table 3 Pre to posttreatment clinical changes in non-dysphonic patients

Clinical outcomes	Pre-treatment	3 months	*p* value	6 months	*p* value
Reflux symptom score					
Otolaryngological score	60.42 ± 42.46	28.02 ± 33.83	0.001	35.92 ± 41.29	NS
Digestive score	43.58 ± 33.80	19.88 ± 24.25	0.001	27.19 ± 39.68	NS
Respiratory score	16.02 ± 17.79	7.65 ± 13.19	0.006	8.81 ± 13.60	NS
RSS—score total	120.02 ± 75.87	55.56 ± 63.01	0.001	71.92 ± 86.20	NS
Reflux sign assessment					
Oral score	5.72 ± 2.23	4.60 ± 1.84	NS	5.00 ± 1.84	NS
Pharyngeal score	10.60 ± 3.73	7.50 ± 3.85	0.001	6.32 ± 4.05	NS
Laryngeal score	13.10 ± 4.81	6.10 ± 4.60	0.001	5.09 ± 5.72	0.030
RSA—total score	28.05 ± 8.03	18.30 ± 7.19	0.001	16.18 ± 8.00	NS

NS non-significant, *RSA* reflux sign assessment, *RSS* reflux symptom score

Table 4 Pre to posttreatment acoustic changes in dysphonic patients

Acoustic measurements	Pre-treatment	3-month	*p* value	6-month	*p* value
Percent jitter	2.12 ± 1.27	1.92 ± 1.11	0.042	2.46 ± 1.49	NS
Percent shimmer	6.68 ± 2.86	5.69 ± 1.97	0.004	6.15 ± 2.13	NS
Noise-to-harmonic ratio	0.20 ± 0.10	0.18 ± 0.08	0.035	0.20 ± 0.10	NS

NS non-significant

Table 5 Pre to posttreatment acoustic changes in non-dysphonic patients

Acoustic measurements	Pre-treatment	3-month	*p* value	6-month	*p* value
Percent jitter	2.48 ± 1.74	2.10 ± 1.29	NS	1.99 ± 1.32	NS
Percent shimmer	6.52 ± 3.24	5.68 ± 2.46	NS	5.31 ± 1.74	NS
Noise-to-harmonic ratio	0.18 ± 0.08	0.18 ± 0.08	NS	0.17 ± 0.06	NS

NS non-significant

Table 6 Responders to treatment at 6 months

Groups	Therapeutic response	Definition	*N*	%
Dysphonic	Complete response	≥ 80% RSS reduction or RSS < 13	10	20.4
	High response	60–79.9% RSS reduction	15	30.6
	Moderate response	40–59.9% RSS reduction	9	18.4
	Mild response	20–39.9% RSS reduction	5	10.2
	No response	< 20% RSS reduction	10	20.4
Non-dysphonic	Complete response	≥ 80% RSS reduction or RSS < 13	16	26.7
	High response	60–79.9% RSS reduction	19	31.7
	Moderate response	40–59.9% RSS reduction	12	20.0
	Mild response	20–39.9% RSS reduction	8	13.3
	No response	< 20% RSS reduction	5	8.3

RSS reflux symptom score

The primary limitations of the present study are the design (uncontrolled study) and the relatively small number of patients in each group. Moreover, the RSA was validated in only one study. The main strengths of the study are the use of HEMII-pH and, therefore, the consideration of acid, weakly acid and alkaline LPR patients, and the 6-month follow-up. Authors of previous studies only considered acid LPR (dual-probe pH monitoring) and limited the exploration of usefulness of acoustic parameters over the first 3 months of treatment. Other approaches could be evaluated in future studies including the speech therapy in LPR patients with dysphonia. Indeed, we observed many patients with voice breaks or supraglottic activity, which may be reduced with adequate speech therapy.

Conclusion

Acoustic measurements can be used as objective indicators of treatment in patients with LPR and self-reported dysphonia. The evolution of acoustic parameters was consistent with the evolution of symptoms and findings. The usefulness of acoustic parameters in LPR patients without dysphonia is still not demonstrated.

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Declarations

Conflict of interest Authors have no conflict of interest.

Research involving human participants and/or animals IRB approved the study protocol (CHUB2020-12). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from patients enrolled in the study. Electronic informed consent was obtained from all individual participants.

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