Are the Acoustic Measurements Reliable in the Assessment of Voice Quality? A Methodological Prospective Study

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Summary: Objective. Acoustic parameters are widely used as voice quality therapeutic outcomes in many laryngological diseases. The aim of this study is to explore the impact of changes in the nature and duration of the analyzed time interval and the vowel choice on the significance of the acoustic measurements used as therapeutic outcomes in two different diseases.

Study Design. A prospective case series.

Material and Methods. From September 2013 to January 2018, patients with laryngopharyngeal reflux (LPR) disease were recruited and treated with pantoprazole, diet, and behavioral changes for 3 months. The reflux symptom index and reflux finding score were used for both diagnosis and assessment of treatment effectiveness. Simultaneously, patients with early idiopathic Parkinson's disease (IPD) were enrolled and benefited from a levodopa challenge test. An Iowa Oral Performance Instrument was used for objective outcomes in the assessment of levodopa effectiveness on muscular strength of IPD patients. Acoustic measurements were performed in both groups pre- and postmedication intake at different time intervals, including the "most stable" time intervals of 1 second, 2 seconds, 3 seconds, 4 seconds, and 5 seconds and a 1 second-time interval positioned at mid-production. We also measured acoustic parameters on the entire signal of three vowels and on the signal of each vowel being taken separately.

Results. A total of 80 LPR and 19 IPD patients met our inclusion criteria and completed the study protocol. LPR and IPD patients had significant clinical improvements throughout treatment, according to reflux symptom index, reflux finding score, and Iowa Oral Performance Instrument scores. The acoustic analysis revealed that acoustic parameters significantly improved from pre- to post-treatment and varied across methods used for measurement. The duration and position of the analyzed time interval in the production and the vowel on which the acoustic measures were made yielded considerable differences in the results.

Conclusion. Depending on the time interval over which the acoustic parameters are measured, the clinically demonstrated effect of the medication may or may not be statistically demonstrated irrespective of the disease. According to the results of this study and regarding the lack of standardization of acoustic measurement methods, a line of thought is proposed to bypass the interval selection problem.

Key Words: Laryngopharyngeal reflux−Parkinson−Acoustic−Voice−Method.

INTRODUCTION

The assessment of voice quality (VQ) is a multidimensional approach requiring the evaluation of all subjective and objective aspects of the voice. As proposed by many international societies, the basic protocol of VQ evaluation includes the following five dimensions: visual analysis (posture, vocal fold videolaryngostroboscopy), patient self-assessment, practitioner perceptual evaluation, aerodynamic, and acoustic measurements.[1−3] These five dimensions are all addressed in VQ evaluation because they are independent from one another and provide a variety of information to the practitioner.[4] In clinical practice, VQ assessment is usually used for the characterization of patient dysphonia at baseline[5] and for therapeutic outcomes.[6,7] Acoustic measurements are one of the most widely used objective parameters because they are very sensible for the detection of subtle voice changes, which remain inaudible to humans.[8] In laryngology, acoustic measurements are especially used as indicators of the efficiency of speech therapy, medical or surgical treatments in many conditions (ie, nodules,[9] polyps,[10] laryngopharyngeal reflux,[11] and or aging voice).[12] Furthermore, some acoustic measures are included in the calculation of many multidimensional scores, such as the dysphonia severity index[13] or the acoustic voice quality index,[14] that are useful in some public health systems to obtain reimbursement of speech therapy.[15]

In two recent systematic reviews focusing on the evolution of acoustic measurements throughout treatment of laryngopharyngeal reflux (LPR) and idiopathic Parkinson's disease (IPD), it was reported that the method used for the

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measurement of acoustic parameters (ie, vowel types; number of samples; and selection of the time interval over which the acoustic parameters are measured) significantly varies between studies, which is associated with controversial results and unclear conclusions.[6,7] In these two diseases, most clinical studies reported significant improvements of acoustic measurements from pre- to post-treatment, but the acoustic parameters identified as the most useful therapeutic outcomes significantly differ from one study to another. These controversial results have led us to conduct a preliminary methodological study to assess the impact of the analyzed time interval on the significance of acoustic measurements used as LPR therapeutic outcomes.[16] In this study, we found that, depending on the time interval over which the acoustic parameters are measured, the potential effect of the treatment may or may not be statistically demonstrated. Nevertheless, this preliminary study was conducted on a small cohort of patients and was a single-disease trial, which did not exclude a potential impact of the disease itself on the results.[16]

The aim of this study is to explore the impact of changes in the nature and duration of the analyzed time interval and the impact of vowel choice on the significance of acoustic measurements in two different laryngeal conditions.

MATERIALS AND METHODS

Population characteristics

From September 2013 to January 2018, patients with LPR-related symptoms were recruited from the Otolaryngology − Head and Neck Surgery department of EpiCURA hospital. LPR diagnosis was performed using the French version of the Reflux Symptom Index (RSI) >13 and Reflux Finding Score (RFS) >7,[17–19] considering the response to an empirical treatment (pantoprazole 20 mg, twice daily), diet, and behavioral changes. RSI and RFS are validated clinical tools that rate symptoms and signs of LPR, respectively. These scores are concurrently used for LPR diagnosis and assessment of the therapeutic response.[11,20] They can be used to identify responder and nonresponder patients and adapt their treatments.[21,22] In this study, as in many previous publications,[23] responder patients were defined as patients with post-treatment RSI <13 & RFS <7 and were considered as LPR patients. The diagnosis of those with RSI ≥13 or RFS ≥7 at the end of treatment was based on positive impedance-pH monitoring. In this study, only patients with a clear LPR diagnosis were included.

In the same period, patients with IPD-related symptoms were recruited from the Neurology department of the same hospital. The diagnosis of IPD was based on symptoms and signs, as well as a DatScan in doubtful cases.[24] To confirm the diagnosis, patients had to have significant clinical improvement 45 minutes after the intake of a standardized dose of levodopa (375 mg, levodopa challenge test). Moreover, these patients were treated and followed by the neurologist for 6−36 months after the levodopa challenge test, and all positively responded to the treatment, thereby supporting the diagnosis.

Irrespective of the disease, for inclusion, patients had to suffer from dysphonia exclusively related to the underlying disease. Thus, subjects with confounding cofactors for illness diagnosis, VQ assessments, and therapeutic response were excluded (Table 1). The protocol of the study has been approved by the ethics committee of EpiCURA Hospital (ref.2015/99).

Clinical assessments

Laryngopharyngeal reflux patients

The primary clinical outcomes used for the treatment effectiveness are the French versions of RSI and RFS scores.[17,19] RSI is a self-administered nine-item questionnaire. The scale for each individual item ranges from 0 (no problem) to 5 (severe problem), with a maximum total score of 45. RFS is an eight-item clinical severity scale based on findings during fiberoptic laryngoscopy. The scale ranges from 0 (no abnormal findings) to a maximum of 26 (worst score possible). Patients completed the RSI at baseline and again at 3 months post-treatment. To determine the RFS score, a senior laryngologist performed videolaryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) in a blind manner in response to patient complaints (RSI).

Patients with idiopathic Parkinson's disease

A senior neurologist assessed the patient's clinical evolution throughout the levodopa challenge test and judged the response to levodopa. In addition to the subjective clinical examination, the Iowa Oral Performance Instrument (IOPI, IOPI Medical) was used as an objective outcome of the

TABLE 1.
Exclusion Criterias

Exclusion Criteria
Psychiatric illness altering the judgment
Upper respiratory tract infections (last month)
Antacid treatment already started
Significant cervical surgery
Chest or Head and Neck radiotherapy
Significant laryngeal trauma
Vocal cord paralysis/paresis
Benign vocal fold lesions
Pharyngolaryngeal malignancy
Treated asthma (corticosteroid inhalation)
Chronic obstructive pulmonary disease (Gold II to IV)
PPI or L-Dopa hypersensitivity
Untreated thyroid disease
Prior antireflux surgery
Chemical exposure causing laryngitis
Moderate of Severe drinker/alcoholics (chronic pharyngitis)
Chronic laryngitis < systemic disease
Pregnant
Lactating women

Abbreviations: PPI, proton pump inhibitors.

evolution of the orofacial muscular strength throughout the levodopa challenge test. IOPI is a clinical instrument that usually measures strength of the tongue, lip, and cheek muscles. The units displayed are kilopascals (kPa), based on the internationally recognized unit of pressure, the pascal (Pa). Recently, the IOPI was proposed as an objective outcome tool in the assessment of levodopa efficacy in IPD.[25]

Voice quality evaluations

Visual analysis, patient self-assessment, practitioner perceptual evaluation, and aerodynamic measurements have been conducted in both patient groups. However, because this study aims to focus on reliability of acoustic measurements, these results were not considered in the present paper.

Concerning acoustic measurements, in addition to the exclusion criteria, patients were initially checked for many cofactors that can impact the acoustic voice quality (beginning of infection, exposure to laryngeal irritant over the past few days, reflux episodes, etc). If there was any doubt, the patient was excluded. Patients were instructed to produce three sustained vowels (/a/) in a maximum phonation time. Voice recordings were performed at baseline and again after 3 months of treatment (LPR, group 1), or at baseline and again 45 minutes after levodopa intake (IPD, group 2) in a sound-treated room by the same physician, with a high-quality microphone (Sony PCM-D50; New York, New York) placed at a distance of 30 cm from the patient's mouth. Acoustic measurements were carried out using MDVP software (KayPentax, Montvale, New Jersey) and included Fundamental frequency (F0), 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), Noise Harmonic Ratio (NHR), Voice Turbulence Index (VTI), and Soft Phonation Index (SPI). The flowchart of the study is available in Figure 1.

The evolution of acoustic measurements from pre- to postmedication intake was analyzed using 10 different acoustic time intervals. Thus, from the same voice samples, the acoustic parameters were measured on the following vowel intervals (Figure 2):

1) 1-second interval positioned at mid-production of the three vowels (mean of the three vowel values);
2) "Most stable" time intervals (exhibiting the lowest jitter percent, shimmer percent, and NHR values) of 1-second, 2-second, 3-second, 4-second and 5-second duration of the three vowels (mean of the three vowel values);
3) Entire acoustic signal of the first vowel;

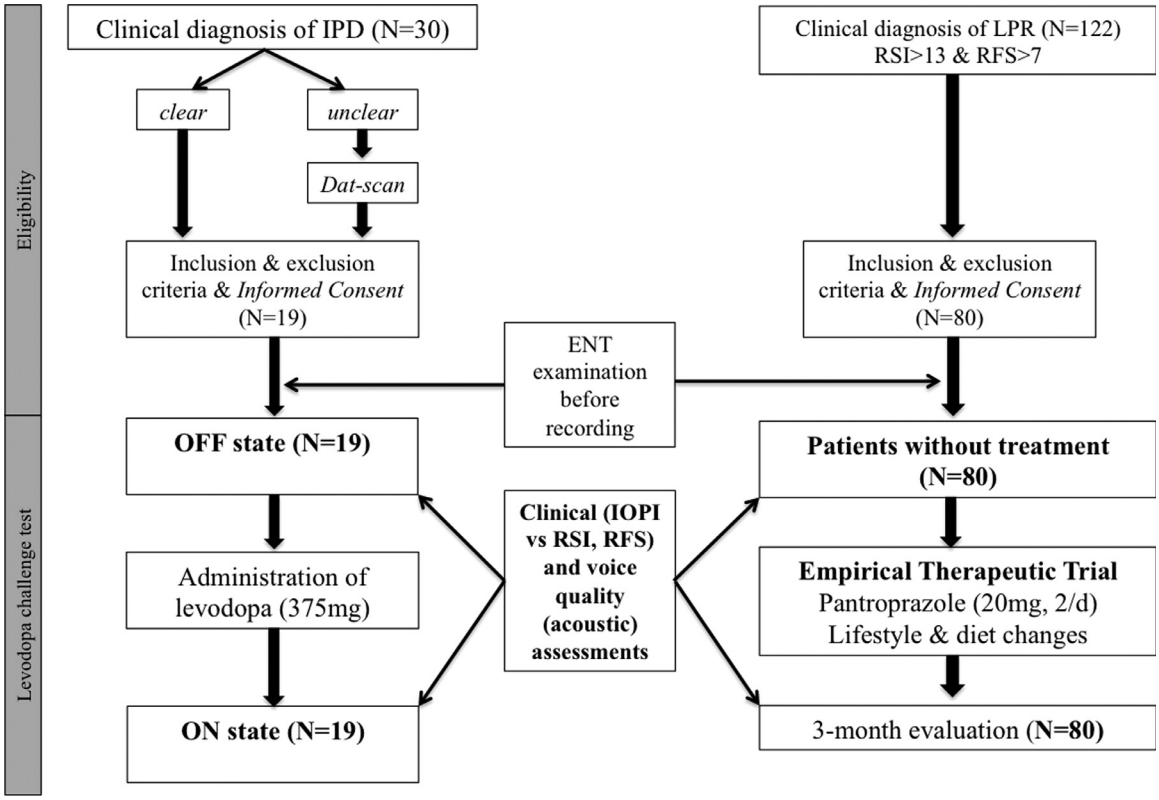

FIGURE 1. Flowchart of the study. LPR and IPD patients have benefited from both clinical (IPD: IOPI; LPR: RSI, and RFS) and voice quality evaluations at baseline and after the intake of medication. ENT, ear, nose, and throat; IOPI, Iowa oral performance instrument; IPD, idiopathic Parkinson's disease; LPR, laryngopharyngeal reflux; RFS, reflux finding score; RSI, reflux symptom index.

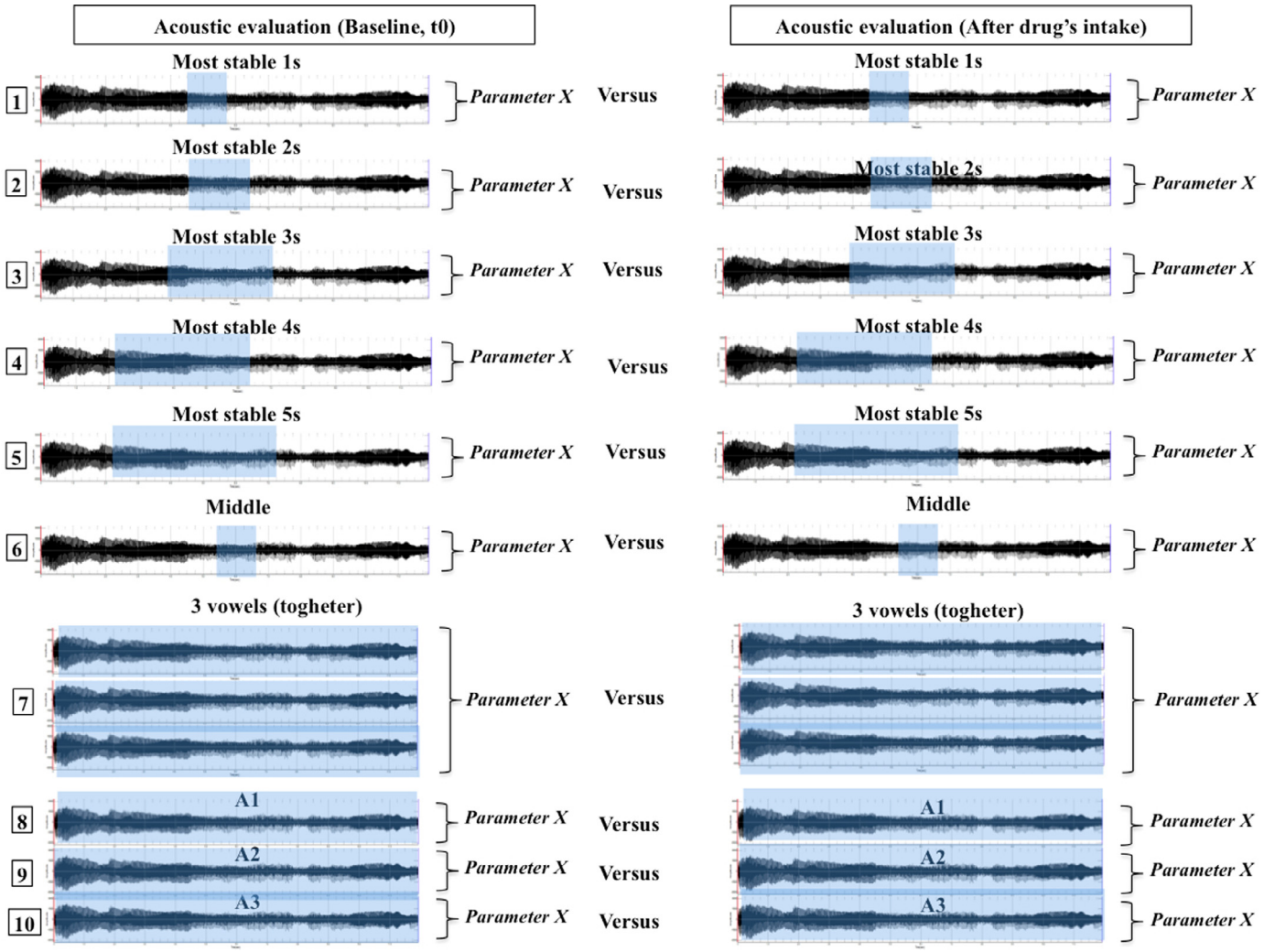

FIGURE 2. Acoustic analyses. Acoustic parameters measured in patients before and after medication intake were analyzed using ten different time intervals, including a 1-s interval positioned at mid-production, as well as 5 'most stable' (i.e., exhibiting the lowest jitter percent, shimmer percent, and NHR values) time intervals of a 1-s, 2-s, 3-s, 4-s and 5-s duration; the first vowel (excluding the second and third vowels); the second vowel (excluding the first and third vowels); the third vowel (excluding the first and the second vowels); and the entire acoustic signal of the three sustained vowels. All patients included in this study had significant clinical improvement.

4) Entire acoustic signal of the second vowel;
5) Entire acoustic signal of the third vowel;
6) Entire acoustic signal of the three sustained vowels.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS version 22.0; IBM Corp. Armonk, New York). In all statistical tests, a significance level of 0.05 was adopted. Changes in clinical and acoustic parameters from pre- to postmedication intake were calculated using Wilcoxon matched-pairs signed-rank tests, and results were compared across time intervals.

RESULTS

One hundred and twenty-two outpatients with LPR and 30 patients with early IPD were recruited. From these patients, 80 LPR and 19 IPD patients met the inclusion criteria and completed the study. The patient characteristics are described in Table 2.

Clinical evolution

Laryngopharyngeal reflux patients

The mean values of RSI and RFS scores significantly decreased from baseline to post-treatment ($P = 0.001$; Wilcoxon test), as seen in Table 2. After treatment, 59 of the 80 patients exhibited a reduction of both RSI and RFS below the thresholds considered as pathological. Among the nonresponder patients, the LPR diagnosis was confirmed using additional examinations. All patients had a minimum of five-point individual improvement of aggregate RSI and RFS scores.

Idiopathic Parkinson's disease patients

The neurologist observed a significant subjective clinical improvement in all patients. According to Wilcoxon test,

TABLE 2.
Clinical Characteristics of Patients

	LPR	IPD
Mean age (y)	51.30 ± 16.99	70.56 ± 2.55
BMI (kg/m^2)	26.36 ± 4.89	26.53 ± 1.30
Gender (F/M)	40/40	8/11
RSI (baseline)	22.03 ± 6.78	–
RFS (baseline)	10.65 ± 2.38	–
RSI (post-treatment)	8.93 ± 6.13	–
RFS (post-treatment)	4.88 ± 3.16	–
Hoehn & Yahr (baseline)	–	1.11 ± 0.33
IOPI tongue (baseline)	–	42.74 ± 14.42
IOPI lips (baseline)	–	16.69 ± 7.34
IOPI left jaw (baseline)	–	20.02 ± 5.93
IOPI right jaw (baseline)	–	17.39 ± 6.40
IOPI tongue (post-treatment)	–	43.02 ± 13.62
IOPI lips (post-treatment)	–	22.79 ± 9.61
IOPI left jaw (post-treatment)	–	21.74 ± 7.75
IOPI right jaw (post-treatment)	–	24.65 ± 8.27

Abbreviations: F/M, female/male; IOPI, Iowa Oral Performance Instrument; IPD, idiopathic Parkinson disease; LPR, laryngopharyngeal reflux; RFS, reflux finding score; RSI, reflux symptom index.

IOPI measurements (available in Table 2) significantly increased throughout the levodopa challenge test for lips ($P = 0.001$), right cheek ($P = 0.001$), and left cheek ($P = 0.008$) in all patients.

Acoustic measurements

Tables 3 (LPR) and 4 (IPD) describe the *P* values characterizing the pre- and post-treatment comparisons of the mean values of acoustic parameters, according to the time interval over which the acoustic parameters were measured.

In LPR disease, performing the acoustic measures over the 1 second "most stable" time interval led to a significant improvement of five acoustic parameters from pre- to post-treatment, namely, PFR, STD, Shim, APQ, and sAPQ. Of these acoustic parameters, only Shim and APQ significantly improved after treatment in the "most stable" 2 seconds, 3 seconds, 4 seconds, 5 seconds time intervals, mid-signal or over the entire signal (Table 3). Note that F0 and noise-related measurements are the only ones parameters that do not vary regarding the method of measurement.

In IPD, the analysis based on the utilization of the different "most stable" time intervals exhibited substantially different improvements of acoustic measurements. No acoustic parameter systematically improved with the treatment regardless of the different intervals used for measurement. Focusing on the impact of vowel choice to assess the evolution of acoustic measures, we only observed significant improvements of vAm and sAPQ when selecting the second vowel (Table 4).

Irrespective of the disease, depending on the selection of the time interval over which the acoustic parameters are measured, the clinically demonstrated effect of the treatment may or may not be statistically demonstrated.

DISCUSSION

The development of acoustic measurements in the mid-20th century led to great enthusiasm about the improvement of VQ evaluations. Over the past few decades, many acoustic programs have been progressively developed and used in a large number of studies.[6,7] Overall, many authors support that acoustic parameters are useful for studying VQ evolution with treatment because they provide objective information about the vibratory process of the vocal folds.[26–28] However, acoustic measurements are very sensitive to many cofactors, such as speech intensity, the type of voice sample on which the measurements are made, hormonal climate, medication, and many other biological factors.[29–31] Despite the increased interest of researchers in the extrinsic determinants impacting the acoustical voice signal, very few studies assessed the impact of the method used to measure acoustic parameters on the acoustic results.[25,32]

However, to date, there is no consensus about the most appropriate method to measure acoustic parameters from a voice sample of dysphonic patients. In the LPR literature, approximately 11 different methods (ie, duration and place of time interval, vowel duration, algorithm, etc) have been used in the 17 studies on the evolution of acoustic parameters, along with treatment.[6] In addition, it seems that a few authors did not provide information regarding the method that they used which supports a lack of interest in the impact of the method on the measurements. The same analysis has been echoed in the Parkinson's literature, with additional factors of variability including the use of different speech samples (/i/ vs /a/ vs /e/ vs /u/ vs connected speech).[7] In the 26 trials using acoustic parameters as a voice research tool, 16 different methods were applied,[7] and nine authors did not provide methodological information.[7]

In the present study, our analyses performed on same patients, same speech signals, same computer routines, and same statistical procedures showed that when the time interval or the vowel used for the measurements differ, the output of the analysis is drastically impacted. These results confirm that it is not possible to compare studies if their methods of acoustic measurements are not similar. In LPR group, an exception could concern F0 and noise-related measurement which is the only one parameter that do not vary regarding the method of measurement. The F0 was measured by MDVP as the *average F0*, which is the average of all F0 values over the signal length (=1s vs 2 vs 3s, etc). For this reason, some variations of F0 are less susceptible to be highlighted by the F0 values but are more easily detected with F0 short-term perturbation cues (which are dedicated to this kind of measurement). This explanation concerns LPR patients who have a good neuromuscular control of

TABLE 3.
PValue of the Pre- to Post-treatment Comparisons of Mean Values of Acoustic Parameters of LPR Patients According to the Time Interval Over Which the Acoustic Parameters Were Measured

Acoustic Parameters	1s		2s		3s		4s		5s		Mid		3 Vowels		A1		A2		A3	
Fundamental Frequency																				
F0	155.08	155.11	156.77	155.68	156.47	153.47	156.34	153.28	156.97	152.43	155.95	151.45	155.14	154.22	155.40	155.47	155.08	155.11	160.24	156.49
F0 short-term perturbation																				
Jitt	1.39	1.41	1.61	1.71	1.71	1.55	1.86	1.61	**1.95**	**1.64**	**2.54**	**2.34**	**2.63**	**2.39**	1.32	1.22	1.39	1.41	**1.54**	**1.47**
RAP	0.82	0.83	0.98	1.01	1.03	0.92	1.11	0.96	**1.17**	**0.98**	1.51	1.40	**1.56**	**1.42**	0.78	0.74	0.82	0.83	**0.91**	**0.87**
PPQ	0.81	0.86	0.99	1.04	1.03	0.93	1.12	0.96	**1.17**	**0.99**	1.56	1.45	**1.59**	**1.46**	0.79	0.76	0.81	0.86	**0.93**	**0.90**
sPPQ	1.16	1.40	1.47	1.73	1.60	1.27	1.71	1.38	**1.86**	**1.52**	2.57	2.33	2.45	2.31	1.05	1.07	1.16	1.40	1.22	1.23
F0 mid-term perturbation																				
PFR	**3.11**	**2.85**	**3.75**	**3.33**	**3.88**	**3.17**	4.08	3.33	**4.36**	**3.45**	5.43	4.62	**5.33**	**4.71**	2.95	2.86	**3.11**	**2.85**	3.18	2.86
STD	**3.22**	**3.08**	**4.35**	**3.87**	**4.81**	**3.03**	5.11	3.36	**5.37**	**3.87**	8.07	6.56	7.51	6.70	2.79	2.87	**3.22**	**3.08**	**3.17**	**3.30**
vF0	2.03	1.92	**2.79**	**2.35**	**2.93**	**1.97**	**3.24**	**2.15**	**3.37**	**2.48**	**5.20**	**4.27**	4.54	4.05	1.72	1.81	2.03	1.92	**1.89**	**1.78**
Intensity short-term perturbation																				
Shim	**5.06**	**4.51**	**5.49**	**4.96**	**5.62**	**5.00**	**5.91**	**5.08**	**6.10**	**5.30**	**7.57**	**6.36**	**7.17**	**6.63**	**4.78**	**4.48**	**5.06**	**4.51**	4.63	4.86
APQ	**4.29**	**3.68**	**4.51**	**4.02**	**4.59**	**4.01**	**4.75**	**4.08**	**4.86**	**4.23**	**5.67**	**4.94**	**5.65**	**5.23**	3.91	3.85	**4.29**	**3.68**	3.80	3.94
sAPQ	**7.91**	**7.23**	**8.17**	**7.74**	8.10	7.65	8.12	7.65	8.47	7.73	8.49	8.14	**9.77**	**8.75**	7.32	7.09	**7.91**	**7.23**	7.37	6.96
Intensity mid-term perturbation																				
vAm	13.52	13.01	**13.93**	**13.18**	13.45	12.58	**13.86**	**12.43**	**14.07**	**12.54**	**13.59**	**12.50**	**16.35**	**14.59**	**13.67**	**11.72**	13.52	13.01	13.10	12.01
Noise-related measurements																				
NHR	0.14	0.14	0.15	0.16	0.15	0.15	0.16	0.15	0.16	0.15	0.19	0.18	0.19	0.18	0.14	0.14	0.14	0.14	0.14	0.15
VTI	0.05	0.05	0.24	0.05	0.18	0.05	0.14	0.05	0.13	0.05	0.05	0.05	0.05	0.05	0.05	0.13	0.05	0.05	0.05	0.05
SPI	18.12	17.33	17.84	17.20	17.96	17.29	17.77	17.44	17.66	17.61	16.90	17.23	18.02	17.59	17.02	16.44	18.12	17.33	18.96	18.39

A1, 2, 3 = first vowel A, second vowel A and third vowel A. **Bold** = *P* value pre to post-treatment <0.05.
Abbreviations: APQ, Amplitude Perturbation Quotient; F0, Fundamental frequency; Jitt, Jitter percent; LPR, laryngopharyngeal reflux; NHR, Noise Harmonic Ratio; PFR, Phonatory Fundamental Frequency Range; PPQ, Pitch Perturbation Quotient; RAP, Relative Average Perturbation; Sapq, Smoothed Amplitude Perturbation Quotient; Shim, Shimmer percent; SPI, Soft Phonation Index; sPPQ, Smoothed Pitch Perturbation Quotient; STD, Standard Deviation of F0; vAm, Peak-to-Peak Amplitude Variation; vF0, Fundamental frequency variation; VTI, Voice Turbulence Index. In bold, the significant *P* value ($P < 0.05$).

TABLE 4.
P Value of the Pre- to Post-treatment Comparisons of Mean Values of Acoustic Parameters of IPD Patients According to the Time Interval Over Which the Acoustic Parameters Were Measured

Acoustic Parameters	1s		2s		3s		4s		5s		Mid		3 Vowels		A1		A2		A3	
Fundamental Frequency																				
F0	137.95	140.43	137.24	140.75	139.17	140.67	138.60	140.56	138.22	105.04	143.21	140.01	**143.06**	**139.87**	136.36	142.44	137.95	140.43	143.13	135.40
F0 short-term perturbation																				
Jitt	1.29	0.99	2.79	1.14	**3.19**	**1.43**	2.99	1.75	3.17	1.80	2.48	2.03	**1.32**	**1.19**	1.29	1.55	1.29	0.99	1.37	0.94
RAP	0.74	0.57	1.72	0.66	1.99	0.84	1.83	1.02	1.94	1.05	1.90	1.80	**0.77**	**0.70**	0.76	0.92	0.74	0.57	0.81	0.54
PPQ	0.76	0.61	1.45	0.71	1.65	0.87	1.63	1.06	1.78	1.09	1.60	1.25	0.79	0.70	0.79	0.89	0.76	0.61	0.82	0.55
sPPQ	1.29	0.98	1.38	1.14	2.25	1.37	2.78	1.61	2.39	1.63	2.70	1.72	1.21	1.01	1.19	1.11	1.29	0.98	1.14	0.93
F0 mid-term perturbation																				
PFR	3.21	2.93	4.53	3.28	4.88	3.33	5.10	3.61	5.24	3.55	6.26	4.25	3.18	3.30	3.35	4.29	3.21	2.93	2.94	2.33
STD	3.07	2.55	5.64	3.62	6.10	3.07	6.83	3.63	6.89	3.68	9.47	3.77	2.81	2.82	2.72	3.45	3.07	2.55	2.62	2.26
vF0	2.22	1.71	4.03	2.45	4.40	2.07	4.81	2.40	4.92	2.43	6.62	2.56	1.98	1.89	1.91	2.27	2.22	1.71	1.80	1.57
Intensity short-term perturbation																				
Shim	5.69	4.86	**9.42**	**5.09**	9.94	5.68	9.53	6.00	9.51	6.38	8.24	7.35	**5.71**	**5.09**	5.67	5.70	5.69	4.86	**5.77**	**4.51**
APQ	5.05	4.16	**7.20**	**4.36**	7.26	4.76	7.28	5.01	7.46	5.24	6.93	5.75	**4.87**	**4.47**	4.81	4.93	5.05	4.16	4.74	4.19
sAPQ	**9.49**	**7.02**	**8.83**	**6.87**	**9.63**	**7.76**	**10.25**	**7.94**	**10.04**	**7.79**	11.78	8.27	**8.62**	**7.14**	8.37	7.51	**9.49**	**7.02**	7.97	6.76
Intensity mid-term perturbation																				
vAm	**15.38**	**10.82**	**16.56**	**12.01**	16.78	12.96	**17.07**	**12.01**	17.74	13.35	17.10	14.31	**14.64**	**12.45**	15.26	15.11	**15.38**	**10.82**	13.19	10.73
Noise-related measurements																				
NHR	0.16	0.14	0.21	0.15	0.21	0.16	0.21	0.17	0.22	0.17	0.20	0.19	**0.22**	**0.15**	0.15	0.16	0.16	0.14	0.15	0.14
VTI	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
SPI	16.27	14.23	15.63	14.44	16.59	14.74	16.39	14.73	16.67	15.13	17.17	16.31	16.05	14.91	16.53	14.65	16.27	14.23	15.27	16.13

A1, 2, 3 = first vowel A, second vowel A and third vowel A. **Bold** = *P* value pre to post-treatment <0.05.

Abbreviations: APQ, Amplitude Perturbation Quotient; F0, Fundamental frequency; IPD, idiopathic Parkinson disease; Jitt, Jitter percent; NHR, Noise Harmonic Ratio; PFR, Phonatory Fundamental Frequency Range; PPQ, Pitch Perturbation Quotient; RAP, Relative Average Perturbation; Sapq, Smoothed Amplitude Perturbation Quotient; Shim, Shimmer percent; SPI, Soft Phonation Index; sPPQ, Smoothed Pitch Perturbation Quotient; STD, Standard Deviation of F0; vAm, Peak-to-Peak Amplitude Variation; vF0, Fundamental frequency variation; VTI, Voice Turbulence Index. In bold, the significant *P* value ($P < 0.05$).

laryngeal muscles but is not found in IPD where the patients may have some voice breaks and sudden changes in the muscle tonicity (and the related F0).

The variability of the F0 short-term perturbation cues over the different length intervals could reflect that both LPR and IPD are characterized by variations of the vibratory process over the sustained vowel. In other words, the characteristics of vibratory process may change throughout the sustained vowel, reflecting the occurrence of some events impairing the vibratory dynamic. Thus, the consideration of one portion of the signal (for example the start of the signal) would provide different information than the consideration of another portion of the signal (for example the middle or the end of the signal) due to different pathophysiological mechanisms. This hypothesis could make sense regarding our acoustic analysis, especially about the F0 short-term perturbation measurements.

Although this methodological diversity is not new, nor is the suspicion of its potential influence on the reported observations, to our knowledge it has never been the subject of a specific investigation particularly conducted in many different diseases.

Moreover, according to the two previous systematic reviews, the large majority of authors measured acoustic parameters at 1−3 seconds of a limited vowel signal and only a few physicians used the entire signal of several sustained vowel samples.[7] The limited time available for outpatient examination could partially explain the use of only one vowel sample of a limited time, but it is possible that the rest of the signal may contain subtle information, that is, the inability to maintain the stability of the acoustic signal, impairment in the onset of the voice signal, or instability at the end of phonation time. In this study, the high heterogeneity in acoustic improvements according to the method may be explained by the occurrence of such a phenomenon in LPR and IPD. Rare studies on the architecture of the acoustic signal in IPD[32] and LPR[33] showed that, according to pathophysiological mechanisms underlying dysphonia, the perturbations of the vibratory process can differ with the phonation process. In LPR, with regards to modifications of the biomechanical properties of the tissue on the free edge of the vocal folds, the initiation of vocal vibration can be altered, leading to higher instability in the beginning of voice emission.[33] Concerning IPD, considering the entire signal of the three vowels, we found significant improvement of many acoustic parameters that can reflect, with regards to the other acoustic results, an important heterogeneity of the acoustic values along the entire signal. Olszewski et al also supported the heterogeneity of the acoustic variability of the voice signal with phonation in IPD patients.[32] However, these authors also suggested that the development of an objective sample selection method may have significant impact on the stability and reliability of acoustic voice measurements. Recently, it has been suggested that the end of the vowel sustained in maximum phonation time could be more unstable than the start of the vowel in IPD patients.[33]

These observations strengthen the need to standardize the method used for measuring acoustic parameters. In this context, we suggest that the acoustic measurement should be made on the entire signal of 3 sustained vowels /a/ because this is most representative of the daily patient voice. Another possible way is to consider the acoustic analysis of continuous speech, which could less suffer much influence of time.

This study has strengths and limitations. First, the low number of IPD patients and the clinical heterogeneity of the disease (many clinical profiles of IPD patients) may contribute to the lack of similar acoustic evolution throughout treatment. Second, the use of a high-speed camera could confirm our hypotheses about the stability of the vibratory process along phonation. Third, about LPR, the use of more reliable clinical tools, such as Reflux Symptom Score[34] and Reflux Sign Assessment,[35] would be better for the assessment of both symptoms and signs associated with LPR but, at the time of the study, these tools did not exist or were not validated. Furthermore, the main strength of this study is the focus on two different diseases, which reduces the potential impact of the disease itself on the results. Moreover, we carefully exclude many conditions able to bias the VQ evaluations. Conducting VQ analyses with same investigator, same software, same conditions of recording and with the same material also reduces the risk of evaluation bias.

PERSPECTIVES AND FUTURE DIRECTION

Recently, in LPR,[34] IPD[36] and other diseases, studies increasingly proposed personalized therapeutic management of patients. In this context, and with regard to the results of this study, we tried to develop an alternative per-subject statistical approach that bypasses the interval selection problem. The objective was to identify the most sensitive acoustic parameters that reflect treatment efficiency. After excluding the onset and offset of the sustained vowel (unstable time interval), all successive 1-second intervals of the three /a/ productions before and after medication intake were included in the analysis and compared with adequate statistical analyses (Mann-Whitney, Friedman tests, and Multiple Linear Regression). From these data, we calculated an "informativeness coefficient" for each acoustic parameter, which was defined as the percentage of "cured" patients for whom a particular acoustic parameter significantly improved from pre- to post-treatment. To assess the informativeness coefficient, we also included in the calculation the "worsened" patients from clinical and acoustic standpoints (when the aggravation of both clinical and acoustic assessments was in the same direction). Tables 5 and 6 show the results of this preliminary per-subject analysis, for which changes from pre- to post-treatment in acoustic parameters were analyzed separately for each patient. According to this approach, we may identify a diversity of patient profiles with respect to the amount and nature of the acoustic parameters, which showed significant differences after treatment: (1)

TABLE 5.
Per Subject Analysis for LPR Patients

N	C/R	F0	STD	PFR	Jitt	RAP	PPQ	sPPQ	vFo	Shim	APQ	sAPQ	vAm	NHR	VTI	SPI	RSI pre	RSI post	RFS pre	RFSpost
1	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.008	0.004	NS	22	3	9	5
2	C	.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	21	3	10	4
3	C	.001	0.002	0.016	NS	NS	NS	0.002	0.003	0.028	0.008	0.005	0.001	0.001	NS	.002	15	4	9	1
4	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.044	0.023	0.016	0.001	0.001	0.001	0.001	18	1	13	13
5	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0,001	0.024	0.020	0.038	0.001	31	5	11	3
6	R	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	0.001	15	10	12	11
7	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0,0154	0.001	0.001	0.001	0,0008	NS	NS	22	6	8	4
8	R	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	0.001	15	14	13	6
9	C	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	31	0	11	0
10	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	30	12	9	6
11	R	0.001	NS	0.002	0.001	0.001	0.001	0,0253	NS	0,0008	0,0013	NS	NS	0.001	0.006	0.001	20	24	9	3
12	C	0.001	0.015	0.003	0.019	0.018	0.008	NS	0.025	0.002	0.005	NS	0.020	NS	NS	NS	24	12	10	3
13	R	0.001	0.001	0.001	0.001	0.001	0.001	NS	0.001	0,0007	NS	NS	NS	0,0003	0,0008	NS	17	16	9	2
14	R	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0,0014	0.001	NS	0.001	0.001	26	12	10	8
15	C	0.001	0.001	NS	0.001	0.001	0.001	0.001	0.001	0,0101	NS	0.001	0.001	0.002	NS	0.001	20	10	10	3
16	C	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	17	3	12	2
17	C	0.001	NS	0.028	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0,0011	0.001	NS	0.001	0.001	20	0	14	5
18	C	0.001	NS	NS	0,04	NS	0,03	NS	0,0308	NS	NS	0.001	0.001	NS	0.001	0.001	14	10	10	5
19	C	.010	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0,0002	0.001	0.001	NS	14	2	9	6
20	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	NS	0.001	0.001	32	10	10	8
21	R	0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.001	0.001	20	7	17	10
22	C	0.001	NS	NS	0.001	0.001	0.001	NS	NS	0.001	0.001	0.001	NS	0.001	NS	0.001	31	12	15	6
23	C	0.001	NS	NS	NS	NS	NS	NS	NS	0.001	0.001	0.010	NS	0.001	0.010	0.001	29	5	11	4
24	C	0.001	0.009	0.001	NS	NS	NS	0.001	0.001	0.001	0.001	0.001	0.001	NS	NS	0.001	31	18	11	4
25	C	0.001	NS	NS	NS	NS	NS	NS	NS	NS	0.043	0.001	0.001	NS	0.049	0.007	37	3	10	4
26	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.002	NS	0.001	0.001	0.001	0.013	0.001	21	8	8	2
27	C	0.001	0.001	NS	0.001	0.002	0.001	0.001	0.004	NS	NS	NS	0.007	0.001	NS	0.001	18	7	9	2
28	R	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.004	0.001	16	10	11	12
29	C	0.001	NS	0.001	0.001	0.001	0.001	NS	NS	0.002	0.031	NS	0.027	0.001	0.008	0.001	14	2	9	0
30	C	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.001	0.001	0.034	NS	0.001	0.001	0.001	24	8	11	10
31	C	0.001	0.001	0.001	0.001	0.001	0.001	0.004	0.001	0.004	NS	0.04	0.009	0.002	0.001	0.001	18	14	13	5
32	C	0.001	NS	0.001	NS	NS	NS	NS	0.005	0.004	0.025	NS	NS	NS	0.001	0.001	35	7	12	6
33	C	0.001	NS	NS	0.032	0.046	0.030	NS	NS	NS	NS	NS	0.028	NS	0.001	0.001	39	11	14	2
34	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	0.001	0.001	17	2	13	1
35	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	19	5	11	2
36	C	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	25	6	12	1
37	C	0.001	0.007	0.048	0.039	0.024	0.005	0.048	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.040	28	7	8	3
38	R	.003	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.016	NS	NS	0.003	0.001	21	15	8	5
39	C	0.001	0.001	0.001	NS	NS	NS	NS	NS	0.007	0.001	0.001	0.001	0.001	0.001	0.001	17	9	9	3
40	C	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	0.021	0.002	0.001	0.001	NS	NS	35	8	8	2
41	C	0.001	NS	NS	0.041	NS	0.045	NS	NS	0.001	0.001	0.001	0.001	0.010	NS	NS	24	8	8	7
42	C	0.001	.007	.002	0.001	0.001	0.001	NS	.019	0.001	0.001	0.001	0.001	0.001	.003	.047	20	5	9	3

(*Continued*)

TABLE 5. (*Continued*)

N	C/R	F0	STD	PFR	Jitt	RAP	PPQ	sPPQ	vFo	Shim	APQ	sAPQ	vAm	NHR	VTI	SPI	RSI pre	RSI post	RFS pre	RFSpost
43	C	0.001	0.001	.002	.010	.028	.001	0.001	.001	.010	0.001	0.001	0.001	.001	0.001	.001	20	2	9	6
44	C	0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.001	0.001	0.001	18	13	12	6
45	C	0.001	.001	.029	0.001	0.001	0.001	NS	.020	0.001	0.001	.009	0.001	0.001	0.001	NS	17	7	12	6
46	C	0.001	.002	NS	NS	NS	NS	NS	NS	0.001	0.001	.001	NS	0.001	0.001	.041	18	3	8	3
47	C	0.001	0.001	0.001	0.001	0.001	0.001	.026	.007	.040	NS	0.001	0.001	NS	.003	0.001	18	3	13	6
48	C	0.001	NS	NS	NS	NS	NS	NS	NS	NS	.046	NS	NS	NS	.003	NS	14	3	12	2
49	C	.001	0.001	0.001	0.001	0.001	0.001	0.001	.002	0.001	0.001	0.001	NS	0.001	0.001	0.001	34	5	9	4
50	R	.001	.001	.001	.030	.040	.030	.002	.001	NS	.035	.002	NS	NS	0.001	0.001	27	23	8	4
51	C	0.001	NS	NS	.002	.001	.002	.017	NS	0.001	0.001	.001	0.001	NS	0.001	0.001	34	10	12	5
52	C	0.001	0.001	NS	NS	NS	.049	.006	0.001	.006	.049	0.001	0.001	.010	0.001	0.001	28	6	9	7
53	R	0.001	NS	.018	NS	NS	NS	NS	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	18	14	10	4
54	C	0.001	NS	NS	NS	NS	NS	.045	NS	NS	NS	NS	.003	0.001	NS	0.001	15	13	9	7
55	R	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	.018	0.001	0.001	0.001	17	2	22	16
56	C	NS	NS	NS	NS	NS	NS	NS	NS	.002	.001	NS	NS	.030	.007	0.001	21	3	12	1
57	C	.022	0.001	0.001	.003	.007	.007	.007	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	16	2	11	1
58	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	.003	33	13	15	1
59	C	0.001	.037	NS	NS	NS	NS	NS	NS	0.001	0.001	0.001	0.001	0.001	NS	NS	17	3	8	6
60	R	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	35	14	11	1
61	R	0.001	.001	.004	0.001	0.001	.001	.017	.002	0.001	0.001	NS	NS	0.001	.008	.002	21	13	12	10
62	R	0.001	NS	NS	NS	.009	NS	NS	NS	NS	.028	0.001	.002	0.001	0.001	0.001	14	12	10	12
63	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	.003	0.001	16	9	14	4
64	C	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	.033	0.001	.001	.009	0.001	0.001	18	12	9	2
65	C	.016	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	.012	NS	NS	0.001	NS	.032	23	26	10	8
66	R	.044	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	16	11	11	7
67	R	0.001	NS	NS	NS	NS	NS	NS	NS	.010	NS	.004	NS	NS	.002	0.001	29	15	9	4
68	C	0.001	NS	.030	NS	NS	NS	.005	.002	0.001	0.001	0.001	.001	NS	NS	.011	19	2	11	3
69	R	.025	NS	NS	NS	NS	NS	NS	NS	NS	.021	NS	.027	NS	NS	NS	28	22	11	8
70	C	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	.001	0.001	0.001	14	8	10	2
71	C	.005	NS	NS	.010	.002	.018	NS	NS	0.001	.003	NS	NS	0.001	0.001	NS	32	8	9	4
72	R	0.001	0.001	NS	.011	.013	.004	.006	.009	NS	NS	NS	NS	0.001	.004	NS	18	18	8	5
73	C	0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.001	.002	0.001	18	3	9	6
74	R	0.001	.003	NS	NS	NS	NS	.038	.047	NS	NS	NS	NS	NS	0.001	.007	30	28	14	6
75	R	NS	.014	.011	NS	NS	NS	NS	.020	0.001	0.001	0.001	.006	0.001	0.001	0.001	17	7	13	7
76	C	0.001	NS	NS	.011	.010	.010	NS	NS	0.001	0.001	0.001	NS	.005	0.001	0.001	19	9	10	3
77	C	0.001	NS	NS	NS	NS	NS	NS	NS	0.001	0.001	0.001	.001	NS	0.001	0.001	14	10	8	1
78	C	.034	0.001	0.001	NS	NS	.018	NS	0.001	NS	NS	NS	NS	.024	0.001	0.001	14	3	9	6
79	C	0.001	0.001	.005	0.001	0.001	0.001	0.001	0.001	0.001	0.001	.001	0.001	0.001	NS	.004	20	7	8	6
80	R	NS	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	NS	0.001	0.001	19	18	10	8

LPR patients who are considered as cured after treatment (RSI <13 & RFS <7) are mentioned in the first column. In green the significant acoustic measurement improvement. In red, the significant acoustic measurement worsening.

Abbreviations: APQ, Amplitude Perturbation Quotient, C/R, cured/resistant patient; F0, fundamental frequency, Jitt, Jitter percent, NHR, Noise Harmonic Ratio, NS, nonsignificant; PFR, Phonatory Fundamental Frequency Range, PPQ, Pitch Perturbation Quotient, RAP, Relative Average Perturbation, RFS pre/post, reflux finding score pre/post-treatment; RSI pre/post, reflux symptom score pre/post-treatment; Sapq, Smoothed Amplitude Perturbation Quotient; Shim, Shimmer percent; SPI, Soft Phonation Index; sPPQ, Smoothed Pitch Perturbation Quotient; STD, Standard Deviation of F0; vAm, Peak-to-Peak Amplitude Variation; vF0, fundamental frequency variation; VTI, Voice Turbulence Index.

TABLE 6.
Per Subject Analysis for IPD Patients

N	F0	STD	PFR	Jitt	RAP	PPQ	sPPQ	vFo	Shim	APQ	sAPQ	vAm	NHR	VTI	SPI	IOPI-t0	IOPI-l0	IOPI-r0	IOPI-j0	IOPI-t1	IOPI-l1	IOPI-r1	IOPI-j1
1	NS	0,001	0,028	0,039	NS	0,024	0,004	0,003	NS	NS	NS	0,016	0,001	NS	NS	35	23	16	10	42	23	16	15
2	<,001	<,001	<,001	<,001	<,001	<,001	<,001	<,001	<,001	0,007	NS	NS	<,001	0,001	NS	61	12	23	22	53	12	22	24
3	0,001	0,001	0,005	0,001	0,001	0,001	0,009	0,001	0,001	0,013	0,004	NS	0,001	NS	0,01	31	6	24	13	34	7	19	16
4	0,004	0,001	0,001	0,001	0,002	0,001	0,001	0,001	0,001	0,001	0,012	NS	0,009	0,001	0,013	53	16	18	22	49	20	27	24
5	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0,001	26	6	13	14	21	8	21	18
6	0,001	NS	NS	NS	NS	NS	NS	NS	NS	0,021	0,001	0,004	NS	NS	NS	42	9	25	32	47	11	27	30
7	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,029	0,041	NS	NS	0,001	NS	NS	43	12	10	7	49	13	10	19
8	0,019	NS	NS	0,034	0,026	0,048	NS	NS	NS	NS	NS	NS	0,012	0,001	0,001	52	29	15	8	72	36	15	10
9	0,002	NS	0,005	NS	NS	NS	NS	NS	NS	0,038	0,001	0,001	0,004	NS	0,042	36	26	18	18	33	32	19	20
10	NS	0,005	NS	0,001	0,002	0,001	0,003	0,001	0,001	0,001	0,008	0,045	0,001	0,001	0,047	30	20	33	20	37	27	36	23
11	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	NS	NS	0,002	44	17	19	19	37	23	24	23
12	0,001	NS	NS	NS	NS	NS	NS	NS	0,001	0,001	0,001	0,001	0,001	0,001	0,001	36	20	23	20	50	22	24	20
13	NS	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	0,001	14	15	23	10	30	13	36	24
14	0,005	0,001	0,001	0,001	0,001	0,001	0,026	0,001	0,001	0,001	NS	0,001	0,001	0,006	NS	35	22	12	17	33	25	14	12
15	0,001	0,003	0,008	NS	NS	NS	NS	NS	0,001	0,001	NS	NS	0,001	NS	0,001	21	10	23	19	43	11	30	20
16	0,001	NS	0,017	0,011	0,014	0,001	NS	NS	NS	0,006	0,001	0,001	NS	0,002	0,001	58	18	27	26	46	42	44	44
17	0,001	NS	NS	0,001	0,001	0,001	0,001	0,001	NS	0,021	NS	NS	0,001	NS	0,017	46	9	19	25	48	21	23	30
18	0,001	0,002	0,001	NS	NS	0,028	NS	0,016	0,001	0,001	0,001	0,001	NS	0,001	0,001	51	33	27	12	54	35	31	21
19	0,001	NS	NS	0,006	0,008	0,017	NS	NS	NS	NS	NS	0,019	0,001	0,001	0,001	62	15	15	14	68	26	21	23

In green the significant acoustic measurement improvement. In red, the significant acoustic measurement worsening. IPD patients who clinically improved their muscular strength after L-Dopa intake are also mentioned in the first column.

Abbreviations: APQ, Amplitude Perturbation Quotient; F0, fundamental frequency; IOPIt/l/r/j, Iowa Oral Performance Instrument tongue/lips/right jaw/left jaw; Jitt, Jitter percent; NHR, Noise Harmonic Ratio; NS, nonsignificant; PFR, Phonatory Fundamental Frequency Range; PPQ, Pitch Perturbation Quotient; RAP, Relative Average Perturbation; Sapq, Smoothed Amplitude Perturbation Quotient; Shim, Shimmer percent; SPI, Soft Phonation Index; sPPQ, Smoothed Pitch Perturbation Quotientl; STD, standard deviation of F0; vAm, Peak-to-Peak Amplitude Variation; vF0, fundamental frequency variation; VTI, Voice Turbulence Index.

patients improving in both clinical findings (signs, symptoms, or muscular strength) and acoustic measurements, (2) patients only improving in clinical findings or acoustic parameters, (3) patients worsening in one or both evaluations, (4) patients improving in one and worsening in the other evaluation. Table 7 displays the informativeness coefficients obtained from the individual patient analysis in both LPR and IPD. In both illnesses, we found inconsistencies between acoustic and clinical evolutions. This result is partly due to the fact that we did not assess the same characteristics with same tools. Thus, some patients substantially improved some symptoms or signs, while others did not respond to treatment. This phenomenon is also known in voice quality assessment, where perceptual evaluations often differ from self-evaluations of objective measurements.[4]

This approach is consistent with the current trend to develop personalized management of patients. IPD is known to be heterogeneous among patients regarding the different lesions of the *locus niger* and the related voice disorders and clinical state.[37] In addition, the impact of levodopa on chest and laryngeal muscles and the related voice quality may significantly vary between subjects[38]; supporting the interest in a per-subject analysis. The heterogeneity of the patient profiles also exists in LPR disease, where patients are sometimes divided in two subgroups according to the presence of hoarseness.[23,39]

Future studies are needed to standardize the method for the acoustic measurements to improve the comparisons between studies. The consideration of the entire signal of the sustained vowel could be proposed for considering all potential pathophysiological mechanisms occurring during the vowel emission. In the same way and to avoid the influence of time, the consideration of acoustic analysis on continuous speech (in association with sustained vowel or not) would be a second way for the acoustic analyses. Some tools have been developed for considering multiple acoustic parameters of both sustained vowen and continuous speech. The Cepstral Spectral Index of Dysphonia and the Acoustic Vocal Quality Index are two examples.[40] They consider several acoustic parameters to provide one single score for voice quality, especially sustained vowel and continuous speech part that provides more information about the real vocal use, although less common in acoustic voice quality analyses.[40] Finally, as found in the present study, with the development of the big data collection, the use of a per-subject approach could consist of a third interesting way. The per-subject approach would significantly improve the personalized clinical and therapeutic approaches for many patients. However, the development of this approach should take into consideration the many extrinsic factors that can influence the acoustic voice signal.

TABLE 7.
Informativeness Coefficients

Acoustic Parameters	% LPR	% IPD
Fundamental frequency		
F0	89.7	47.4
F0 short-term perturbation cues		
Jitt	70.7	36.8
RAP	67.2	36.8
PPQ	74.1	42.1
sPPQ	63.8	31.6
F0 mid-term perturbation cues		
PFR	65.5	21.1
STD	67.2	21.1
vF0	67.2	42.1
Intensity short-term perturbation cues		
Shim	81.0	42.1
APQ	81.0	57.9
sAPQ	77.6	36.8
Intensity mid-term perturbation cues		
vAm	74.1	26.3
Noise-related measurements		
NHR	77.6	42.1
VTI	75.9	31.6
SPI	81.0	26.3

Flo, F0, MF0, Fhi, APQ, Shim and SPI have the highest percentage, which correspond to a match between the evolution of clinical findings and acoustic parameters. For IPD patients, APQ and F0 are the most acoustic parameters associated with the evolution of the muscular strength.
Abbreviations: APQ, Amplitude Perturbation Quotient; F0, fundamental frequency; Jitt, Jitter percent, NHR, Noise Harmonic Ratio; PFR, Phonatory Fundamental Frequency Range; PPQ, Pitch Perturbation Quotient; RAP, Relative Average Perturbation; sAPQ, Smoothed Amplitude Perturbation Quotient; Shim, Shimmer percent; SPI, Soft Phonation Index; sPPQ, Smoothed Pitch Perturbation Quotient; STD, standard deviation of F0; vAm, Peak-to-Peak Amplitude Variation; vF0, fundamental frequency variation; VTI, Voice Turbulence Index.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jvoice.2019.08.022.

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