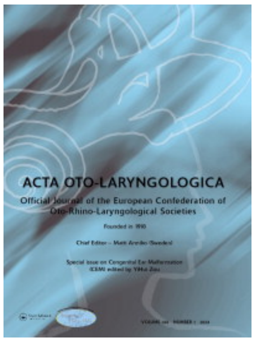

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RESEARCH ARTICLE

Immediate effect of recurrent laryngeal nerve stimulation in patients with idiopathic unilateral vocal fold paralysis

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ABSTRACT

Background: There is a lack of effective treatment for idiopathic unilateral vocal fold paralysis (IUVFP). A better phonation was reported by patients after laryngeal nerve stimulation during our clinical examination.

Objectives: This study aims to investigate immediate effect of recurrent laryngeal nerve (RLN) stimulation on phonation in patients with IUVFP.

Material and Methods: Sixty-two patients with clinically identified IUVFP underwent RLN stimulation with needle electrodes. Laryngoscopy, acoustic analysis, and voice perception assessment were performed for quantitative comparison of vocal function and voice quality before and after the intervention.

Results: Laryngoscopic images showed a larger motion range of the paralyzed vocal fold ($p < .01$) and better glottal closure ($p < .01$) after RLN stimulation. Acoustic analysis revealed that the dysphonia severity index increased significantly ($p < .01$) while the jitter and shimmer decreased after the intervention ($p < .05$). According to perceptual evaluation, RLN stimulation significantly increased RBH grades in patients with IUVFP ($p < .01$). Furthermore, the improvement in voice perception had a moderate positive correlation with the decrease in the glottal closure.

Conclusions and Significance: This study shows a short-term improvement of phonation in IUVFP patients after RLN stimulation, which provides proof-of-concept for trialing a controlled delivery of RLN stimulation and assessing durability of any observed responses.

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Idiopathic unilateral vocal fold paralysis; neuromuscular electrical stimulation; recurrent laryngeal nerve; vocal function; voice quality

Introduction

Unilateral vocal fold paralysis (UVFP) is a common laryngeal disorder and patients with UVFP generally suffer from hoarseness, shortened maximal phonation time, dysphonia, and dyspnea [1–3]. The etiology of UVFP includes iatrogenic injuries (e.g. thyroid surgery), neurological diseases, trauma, tumors, infections, and systemic diseases [4,5]. However, in clinical practice, the initial cause of paralysis may not be identified, which is termed idiopathic unilateral vocal fold paralysis (IUVFP), accounting for about 13.2-65.7% of the patients with UVFP [4,6,7].

Although many efforts have focused on various etiologies contributing to idiopathic paralysis [8,9], the pathophysiology of IUVFP is not well understood, which has implications for targeted interventions and effective improvement of the disease. Since it was reported 29.5–52% of patients with IUVFP could achieve complete or partial recovery within the first year from onset, conservative nonsurgical treatments (including drug therapy, physical therapy, traditional Chinese medicine treatment, and voice training) are generally predominant [10–12]. As a result, the course of IUVFP is usually quite protracted, which has a significant impact on patients' quality of life.

Regardless of etiology, the immobility of the paralyzed vocal fold is likely associated with functional changes in the laryngeal nerve or intrinsic muscles. Neuromuscular electrical stimulation (NMES) is an effective method to increase muscle strength and motion, accelerate nerve regeneration, and prevent atrophy of the paretic muscle [13,14]. It has been applied to patients with UVFP and has been showed to be useful in reducing breathiness and improving vocal control and voice quality [15–17]. However, several studies found that NMES did not have a significant positive effect on improving vocal fold movement and voice acoustics [18,19]. Therefore, the clinical effect of NMES in the treatment of vocal fold paralysis remains uncertain. Especially for IUVFP, experimental and clinical data are still lacking for further evaluation of NMES intervention.

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During our clinical diagnosis of IUVFP, some patients reported laryngeal relaxation and improvement of hoarseness immediately after nerve conduction velocity measurement, in which electrical stimulation was applied [20,21]. Based on this observation, we hypothesized that NMES could improve laryngeal function and voice production in idiopathic cases. The aim of this work was to investigate the immediate effect of recurrent laryngeal nerve stimulation on vocal fold movement, vocal function and voice quality in patients with IUVFP.

Methods

Participants

A total of 62 patients (including 32 males and 30 females with an age of 53.5 ± 16.0 years old), diagnosed with IUVFP at the Throat Clinic of the Second Affiliated Hospital of Xi'an Jiaotong University between March 2021 and April 2023, were recruited and treated with electrical stimulation. Before the study, all participants were confirmed by thoracic CT, thyroid ultrasound, and cranial MRI examinations that they had no history of trauma or surgery and had no other underlying diseases. All patients were treated for the first time and the onset time was less than one year (3.8 ± 6.3 months). According to a power calculation [22], the sample size in this study was enough to show a significance in the statistical analysis with type I error of 0.05 and statistical power of 80%.

Electrical stimulation

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University, and each participant was informed of the possible complications and accidents during the stimulation. Since all intrinsic laryngeal muscles could be activated *via* the stimulation of the recurrent laryngeal nerve (RLN) alone [23], only the RLN stimulation was performed in each patient using needle electrodes (Nihon Kohden Neuropack, Tokyo, Japan).

For each trail, the patient was placed in the supine position with the neck fully exposed. Then, the stimulating electrode was inserted from the trachea-esophageal groove (2 cm below the cricoid cartilage) toward the posterior-lateral of the inferior margin of cricoid cartilage for approximate 2–2.5 cm. To ensure accurate placement of the stimulating electrode, evoked laryngeal electromyography (EMG) of the thyroarytenoid (TA) and posterior cricoarytenoid (PCA) muscles were examined using concentric needle electrodes (Nihon Kohden Neuropack, Tokyo, Japan) but removed during the stimulation.

In this study, a triangular pulse with a short pulse width of 0.2 ms and a low frequency of 1 Hz was used as the stimulus to avoid possible neuromuscular fatigue and damage [14,19]. According to our previous experience, 24 mA current was able to generate stable activation of laryngeal muscles (i.e. TA and PCA). Thus, an electrical stimulation with a constant current was finally performed on each patient for a period of 10 min.

Examinations and data process

To investigate the immediate effect of RLN stimulation, vocal fold movement, vocal function, and voice quality were quantitatively evaluated half an hour before and after the intervention using laryngoscopy, acoustic analysis, and perceptual assessment, respectively.

All patients underwent a high-resolution endoscopic laryngeal examination (XION EndoSTROB, Berlin, Germany) to assess vocal fold movement before and after the RLN stimulation. In this examination, each patient was asked to produce an/i/vowel followed by a quick inhale/sniffing to assess the extent of adduction and abduction of the vocal folds [19,24]. Since vocal fold mobility refers to vocal fold movement toward (i.e. adduction) and away from (i.e. abduction) the glottal midline [24], the maximum range of vocal fold motion can be evaluated based on the changes in the glottal angle from laryngeal adduction to abduction. As shown in Figure 1, the glottal angle (α) between the midline and the line straight from the anterior commissure to the vocal process was measured for each side of the vocal folds (including healthy and paralyzed), similarly as in previous study [25]. The variation in glottal angle (GAV) was then equal to the difference between the glottal angles at the maximum abduction and adduction, i.e.

$$GAV = \alpha_{abduction} - \alpha_{adduction}$$

Assuming that glottal angle variation (GAV) of the healthy vocal fold is the normal value [26], vocal fold movement for each patient was finally quantified as the normalized glottal angle variation (NGAV), i.e. the ratio of the GAV of the paralyzed side to the healthy side as follows

$$NGAV = \frac{GAV_{paralyzed}}{GAV_{healthy}}$$

which could eliminate the differences of individual and phonation. In addition, the pre-phonation closure of the glottis was assessed by measuring the total glottal angle at the maximum adduction (AGC). To reduce bias, the laryngoscopy images were analyzed by the reviewers without knowing the pre- and post- stimulation status. It should be noted that, due to invasive discomfort and image quality, only 36 patients (18 males and 18 females) completed the twice endoscopic examinations and provided valid data.

Acoustic assessment was also performed in all patients before and after RLN stimulation. The subject was instructed to take a deep breath and then to produce the vowel/i/at a comfortable pitch and volume for as long as possible. The jitter, shimmer, maximum phonation time (MPT), and dysphonia severity index (DSI) were calculated and analyzed using voice evaluation software (XION DiVAS, Berlin, Germany) to evaluate the stimulation effect on vocal function.

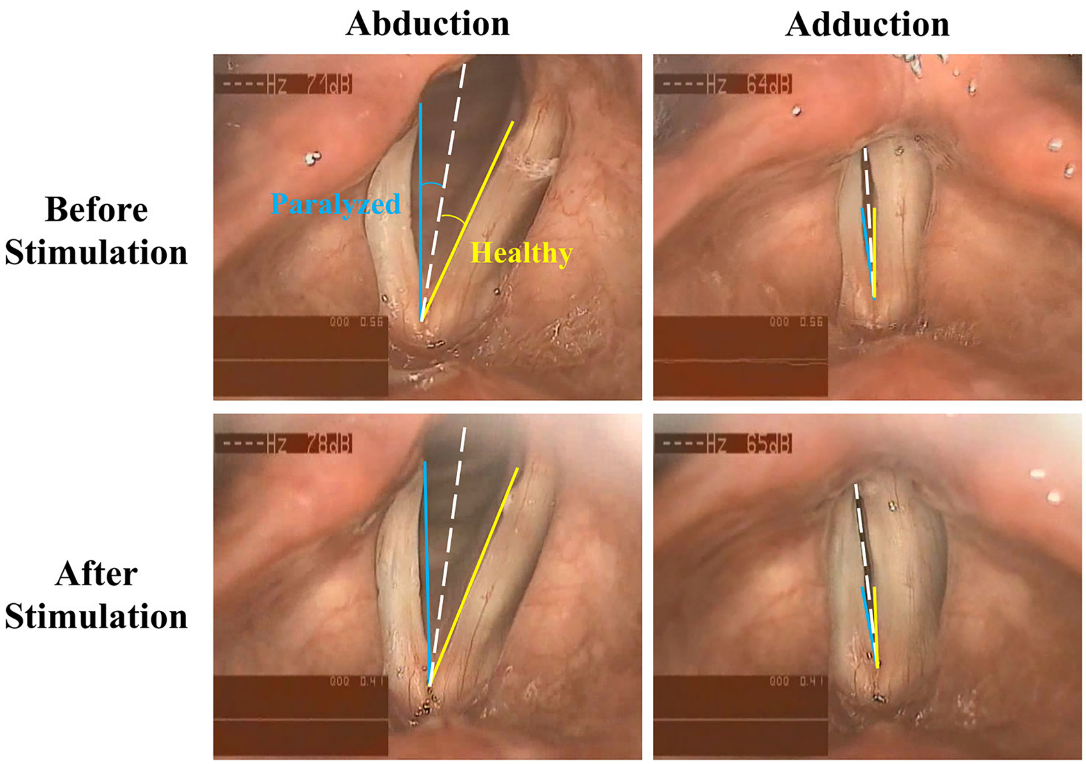

Figure 1. Typical laryngoscopic images before and after recurrent laryngeal nerve stimulation in a male patient. (A) and (B) show vocal fold abduction and adduction before the stimulation, while (C) and (D) show vocal fold abduction and adduction after the stimulation. In each panel, the white dashed line represents the glottal midline, while the yellow and blue solid lines illustrate the other side of glottal angles for the healthy and paralyzed vocal folds, respectively.

For subjective assessment of voice quality, the Roughness, Breathiness, Hoarseness (RBH) scale was used to investigate the changes in voice perception caused by RLN stimulation [27,28]. In the trial, each subject was asked to read a short paragraph ("Boreas and Sun") in natural pitch and volume in Chinese [29]. Then, RBH assessment was performed by an experienced voice specialist and each parameter was rated on a scale of 0-3 with reference to the different degrees of deviation from normal voice (0 - normal voice; 1 - mild degree; 2 - moderate degree; 3 - high degree).

Statistical analysis

Statistical analysis was performed in the MATLAB environment. Firstly, the Shapiro-Wilk test was used to check normal distribution for all measured values. Since almost all data were not normally distributed, the Wilcoxon Signed Ranks Test was performed to compare the differences of each measured value before and after RLN stimulation. Then, the nonparametric Mann-Whitney U test was used to compare the data in the different gender groups. Furthermore, the correlations between the stimulation effects and the different measures were analyzed using linear regression. For better comparison and analysis, all measured values were scaled to a range of [0,1] using the Min-Max normalization method. For all tests, statistical significance was defined as $p < 0.05$.

Results

Immediate effects of RLN stimulation

The statistical values of the selected measures and their differences before and after RLN stimulation are listed in Table 1. For perceptual parameters, all RBH grades were significantly reduced by an average of 0.4 after RLN stimulation, showing a perceived improvement in voice quality with less roughness, breathiness, and hoarseness. In acoustic parameters, DSI increased significantly from an average of −0.223 to 0.588, while MPT only showed little change (<3%) compared with pre-stimulation values. This outcome represented alleviated dysphonia and better phonic function but slight improvement in glottal insufficiency. Jitter and shimmer also decreased by an average of 0.199 and 0.328, respectively, indicating less fluctuation and more regularity in vocal fold vibration. In addition, laryngoscopy images revealed that the average NGAV after the stimulation was significantly higher than the value before the stimulation, while AGC value became smaller after the stimulation, indicating a larger range of the paralyzed vocal fold motion and better closure of the glottis before phonation. In general, all measures (except MPT) showed significant changes after the stimulation, indicating a remarkable and positive effect of the intervention on speech production in patients with IUVFP. Proportionally, at least 60% of patients had improvement in at least one aspect of vocal fold movement, vocal function, and voice quality.

Table 1. Summary data for comparison of the measures before and after RLN stimulation.

Measure	N		Mean ± Standard Deviation	Difference (After-Before)	Wilcoxon Signed Ranks Test		Percentage of Patients with improvement
					Z	p*	
R	62	Before	1.531 ± 0.844	−0.390 ± 0.436	−5.448	**<.001**	67.74%
		After	1.140 ± 0.787				
B	62	Before	1.368 ± 1.019	−0.435 ± 0.574	−4.799	**<.001**	62.90%
		After	0.932 ± 0.832				
H	62	Before	1.660 ± 0.844	−0.431 ± 0.493	−5.280	**<.001**	70.97%
		After	1.229 ± 0.835				
MPT	54	Before	8.827 ± 8.523	0.152 ± 3.379	1.069	.285	59.26%
		After	8.979 ± 8.465				
DSI	49	Before	−0.223 ± 2.055	0.811 ± 1.473	3.606	**<.001**	73.47%
		After	0.588 ± 1.670				
jitter	54	Before	1.039 ± 0.572	−0.199 ± 0.872	−2.559	**.010**	61.11%
		After	0.840 ± 0.736				
shimmer	54	Before	3.325 ± 1.092	−0.328 ± 1.686	−2.036	**.042**	61.11%
		After	2.998 ± 1.281				
NGAV	36	Before	0.264 ± 0.145	0.190 ± 0.116	5.216	**<.001**	97.22%
		After	0.454 ± 0.162				
AGC	36	Before	9.479 ± 4.496	−3.359 ± 3.284	−4.642	**<.001**	80.56%
		After	6.120 ± 3.994				

*$p<0.05$ in bold denote statistical significance. Abbreviations: RLN: recurrent laryngeal nerve; MPT: maximum phonation time; DSI: dysphonia severity index; NGAV: normalized glottal angle variation; AGC: angle of glottal closure.

Table 2. Comparison of stimulation effect on selected measures in different gender groups.

Difference of measure	Mean ± Standard Deviation		Mann–Whitney U-test	
	Male	Female	Z	p*
ΔR	−0.363 ± 0.446	−0.420 ± 0.431	0.801	.423
ΔB	−0.381 ± 0.520	−0.493 ± 0.631	0.769	.442
ΔH	−0.363 ± 0.464	−0.503 ± 0.520	1.272	.203
ΔMPT	0.277 ± 3.594	−0.005 ± 3.159	−0.479	.632
ΔDSI	0.887 ± 1.406	0.717 ± 1.579	0.332	.740
Δjitter	0.073 ± 0.918	−0.538 ± 0.687	3.064	**.002**
Δshimmer	−0.269 ± 1.795	−0.401 ± 1.575	0.444	.657
ΔNGAV	0.187 ± 0.107	0.193 ± 0.127	−0.047	.962
ΔAGC	−2.835 ± 2.621	−3.883 ± 3.841	0.475	.635

*$p<0.05$ in bold denote statistical significance. Abbreviations: MPT: maximum phonation time; DSI: dysphonia severity index; NGAV: normalized glottal angle variation; AGC: angle of glottal closure.

Table 2 shows the statistical comparison of the stimulation effects on the selected measures in different gender groups of subjects. No significant difference was found between male and female groups in the change of any measure (except jitter) before and after the stimulation (Table 2). For jitter, significant changes after stimulation were observed in the female group ($p<.001$, Wilcoxon Signed Ranks Test) but not in the male group ($p=.992$, Wilcoxon Signed Ranks Test). In addition, for most measures (e.g. RBH grades, shimmer, NGAV, and AGC), absolute values of average changes before and after stimulation in the female group were larger than those in the male group.

Correlation between stimulation effects and measures

Because all measures (except MPT) showed significant changes after RLN stimulation, the relationships between the different stimulation effects were analyzed using a simple linear regression model, as listed in Table 3. First, there were strong linear correlations between the changes in R, B, and H values ($p<.001$), indicating a consistent influence of RLN stimulation on the perceptual quality of the voice. In addition, the changes in the RBH grades also had a significant linear correlation with the changes in AGC ($p<.05$), suggesting that the improvement in voice perception may be partly due to better closure of the glottis resulted from the stimulation. For the acoustic parameters, there was a significant linear correlation between the changes in jitter and shimmer ($p<.01$), but no relationship was observed between the acoustic parameters and the perceptual parameters or glottal angles. In addition, the change in AGC was not significantly related to the change in NGAV, which indicated different influences of RLN stimulation on glottal closure and opening.

Table 4 shows the results of multiple linear regression between RLN stimulation effects and pre-stimulation measures. Due to multiple collinearities between R, B, and H scales, mean value of the three scales (i.e. *RBH*) was calculated and used in the multiple regression analysis. Except MPT and NGAV, the regression models for effects on R, B, H, DSI, jitter, shimmer, and AGC were statistically significant ($p<.05$), indicating linear relationships between the stimulation effects and pre-stimulation measures. For example, changes in R, B, and H scales were negatively related with *RBH*, meaning that large improvement in voice quality (i.e. decreasing in R, B, H) was more likely to occur in the conditions with poor perceptual evaluation (i.e. higher R, B, H values). This pattern could also be observed in the relationship between ΔDSI and DSI, Δjitter and jitter, Δshimmer and shimmer, ΔAGC and AGC.

Discussion and conclusion

Inspired by our clinical observations that patients with IUVFP experienced easier phonation and produced better voice immediately after neuromuscular electrical stimulation during laryngeal electromyography examination, this preliminary study was intended to investigate the immediate effect of RLN stimulation based on the results from total 62 patients.

Table 3. Correlation between changes in different measures using a simple linear regression model.

R^2 *	ΔR	ΔB	ΔH	ΔDSI	Δjitter	Δshimmer	ΔNGAV	ΔAGC
ΔR	**1.000**	**0.428**	**0.754**	0.006	0.000	0.003	0.021	**0.110**
ΔB		**1.000**	**0.559**	0.069	0.001	0.056	0.002	**0.118**
ΔH			**1.000**	0.001	0.000	0.004	0.014	0.093
ΔDSI				**1.000**	0.000	0.018	0.047	0.076
Δjitter					**1.000**	**0.198**	0.066	0.033
Δshimmer						**1.000**	0.002	0.019
ΔNGAV							**1.000**	0.029
ΔAGC								**1.000**

*R^2 with statistical significance ($p < 0.05$) are highlighted in bold. Abbreviations: MPT: maximum phonation time; DSI: dysphonia severity index; NGAV: normalized glottal angle variation; AGC: angle of glottal closure.

Table 4. Multiple linear regression between stimulation effects and pre-stimulation measures.

	Standardized coefficients of selected measures before RLN stimulation*							
Stimulation effects	$\overline{RBH}$	MPT	DSI	jitter	shimmer	NGAV	AGC	R^2 *
ΔR	**−0.944**	0.315	−0.556	0.139	0.293	−0.173	−0.023	**0.475**
ΔB	**−0.608**	0.437	−0.395	0.070	0.089	−0.067	−0.186	**0.636**
ΔH	**−0.857**	0.492	**−0.749**	0.171	0.177	−0.232	−0.046	**0.462**
ΔM	−0.357	−0.511	−0.234	−0.007	−0.061	−0.087	0.087	0.314
ΔDSI	−0.490	0.175	**−1.082**	−0.060	0.174	−0.124	−0.010	**0.577**
Δjitter	0.252	0.132	−0.009	**−0.839**	0.033	−0.064	−0.058	**0.629**
Δshimmer	**0.691**	0.243	−0.001	−0.044	**−0.783**	0.189	−0.318	**0.706**
ΔNGAV	0.115	0.083	0.023	−0.389	−0.100	−0.258	0.082	0.231
ΔAGC	−0.362	0.291	**−0.711**	−0.114	0.295	−0.145	**−0.671**	**0.532**

*Coefficients and R^2 with statistical significance ($p < 0.05$) are highlighted in bold. Abbreviations: RBH, mean value of R, B, and H scales; MPT: maximum phonation time; DSI: dysphonia severity index; NGAV: normalized glottal angle variation; AGC: angle of glottal closure.

In this work, laryngoscopy, acoustic analysis, and voice perception were used to qualitatively evaluate the effect of RLN stimulation. The statistical results showed a significant decrease in RBH grades, jitter, shimmer, and AGC, and an increase in DSI and NGAV (see Table 1), suggesting that RLN stimulation is possible to increase vocal fold adduction and abduction, reduce dysphonia and vocal fold vibration irregularity, and improve the quality of voice perception. These results are similar to previous studies on the use of NMES for voice disorders [15–17], and support our clinical observations and confirm the hypothesis that RLN stimulation is a potential method for improving laryngeal function and voice quality in patients with IUVFP.

Because the causes of IUVFP is not known and RLN stimulation will activate all intrinsic laryngeal muscles, underlying mechanisms of RLN stimulation cannot be identified from this study. Nonetheless, some possible cause-effect relationships can still be inferred from the results. First, the decreased AGC suggests better closure of the glottis, which may be related to the improvement in laryngeal muscle strength and tension as a result of electrical stimulation [14]. Then, the better glottal closure contributes to the improvement of voice perceptual quality, as shown by the significant correlation between the changes in RBH and AGC (see Table 3). Moreover, electrical stimulation is also able to improve muscle control [15], which could be a possible cause of the reduced jitter and shimmer and increased NGAV.

When the results of different gender groups were compared, it was found that the changes in all measures (except jitter) were not significant different, indicating that the effects of RLN stimulation were consistent between male and female patients. However, absolute changes in most measures (see Table 2) were slightly larger in the female group than in the male group, which might show better stimulation effects for the female patients. This outcome may be related to differences in the physiological structure of men and women, which need to be investigated in the future.

While multiple regression analysis showed a significant relationship between the stimulation effects and pre-stimulation measures (see Table 4), it implied a possibility of predicting immediate treatment effect based on pre-stimulation examinations. In other words, our results indicated that patients with worse pre-stimulation examinations (e.g. RBH grades, DSI, Jitter, Shimmer, and AGC) may get better improvements in vocal fold movement, vocal function, and voice quality.

As a pilot study, this work shows a significant and positive short-term effect of recurrent laryngeal nerve stimulation on improving vocal fold movement, vocal function, and voice quality in patients with IUVFP. However, due to the difficulties in clinical conditions and patient recruitment, optimal parameters and durable effects of RLN stimulation were not evaluated. Nonetheless, RLN stimulation is still a potential intervention for treatment of IUVFP, which suggests further research to assess long-term effects of a controlled stimulation on subjective and objective improvement of phonation.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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