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Nonselective Reinnervation as a Primary or Salvage Treatment of Unilateral Vocal Fold Palsy

Jean-Paul Marie, MD, PhD; Kevin Hansen, MD; Philippe Brami, MD; Adrien Marronnier, MD; Nicolas Bon-Mardion, MD, PhD

Objectives/Hypothesis: Demonstration of voice improvement and long-term stability following nonselective unilateral laryngeal reinnervation (ULR) in patients with unilateral vocal fold paralysis (UVFP) and severe denervation. A subgroup of patients on whom ULR was performed as a salvage technique following unsuccessful medialization was analyzed separately.

Study Design: Prospective cohort study.

Methods: The ansa cervicalis–recurrent laryngeal nerve anastomosis technique was performed in all patients. Pre- and postoperative voice analysis included voice questionnaires, voice assessment by senior laryngologists using the Hirano Voice Scale, and computer-assisted voice analysis at defined time points over the course of 36 months. Laryngeal electromyography (LEMG) and spirometry were performed before and 1 year after ULR.

Results: Significant linear improvement of mean voice quality over time was observed in the majority of parameters measured in 48 ULR patients and in eight ULR salvage patients. LEMG 1 year after ULR showed new recruitment. Mean voice quality remained stable during follow-up in all ULR patients and in the ULR salvage group.

Conclusions: Nonselective ULR in UVFP is a reliable and stable therapeutic option for patients with high expectations concerning voice quality. The effect is stable in long-term results. It is also a viable option for patients in whom conventional voice surgery failed to improve voice quality. We therefore propose ULR as salvage option in UVFP.

Key Words: Laryngeal reinnervation, unilateral vocal fold paralysis, laryngeal synkinesis, dysphonia.

Level of Evidence: 2b

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INTRODUCTION

Unilateral vocal fold paralysis (UVFP) as a result of recurrent laryngeal nerve (RLN) injury is a common complication of thyroid, thoracic, or skull base surgery and radiation treatment.[1] It may also be of viral or idiopathic origin.[1] RLN injury causes a two-fold problem. The first is incomplete closure of the affected vocal cord due to lack of adduction, and the second is eventual atrophy of the vocal cord, which reduces resistance during attempted closure of the vocal cords. These changes can lead to voice impairment and aspiration.

Treatment of UVFP includes noninvasive as well as invasive procedures. Noninvasive procedures concentrate on compensatory mechanisms from the normal vocal cord through exercises, whereas invasive procedures can be divided into vocal cord augmentation, thyroplasty, arytenoidopexy, as well as reinnervation procedures. Vocal fold augmentation can be done by injection of autologous material (fat) or other materials (e.g., calcium hydroxylapatite).[2] Thyroplasty procedures can be performed by insertion of prosthesis such as the titanium vocal fold medializing implant (Friedrich),[3] expansive polytetrafluoroethylene implant (Gore-Tex),[4] or the Montgomery thyroplasty implant system.[5]

Reinnervation techniques focus on nonselective reinnervation of all the paralyzed laryngeal muscles to increase muscle tone and therefore increase vocal cord resistance necessary for glottic vibration during phonation. The ansa cervicalis-to-RLN anastomosis first described by Crumley and Izdebski,[6] the XII-recurrent anastomosis described by Paniello,[7] and the nerve–muscle pedicle implantation of Tucker[8] are possible approaches.

The objective of this prospective study was to demonstrate improvement and long-term stability of voice following nonselective reinnervation performed as a primary or secondary treatment of UVFP in patients with strong denervation proven by laryngeal electromyography (LEMG). The secondary objective was to demonstrate further voice improvement

From the Department of Otorhinolaryngology–Head and Neck Surgery (J.-P.M., K.H., P.B., A.M., N.B.-M.), University Hospital of Rouen, Rouen, France; Ventilary Handicap Research Group (J.-P.M., N.B.-M.), University of Rouen, Rouen, EA 3830 GRHV, France; and the University Hospital Federation SURFACE, Regenerative surgery in Head and Neck, Amiens (J.-P.M., N.B.-M.), France.

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J.-P.M. was responsible for the study design, acted as an operating surgeon, and wrote the article. K.H. was responsible for data analysis and writing the article. P.B. and A.M. were responsible for the phoniatric evaluation. N.B.-M. acted as an operating surgeon.

J.-P.M and K.H. contributed equally to this work.

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Send correspondence to Jean-Paul Marie, MD, Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital of Rouen, 1 Rue de Germont, 76000 Rouen, France. E-mail: jean-paul.marie@chu-rouen.fr

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after time surpassing direct voice improvement due to fat augmentation attributable to axonal regrowth.

MATERIALS AND METHODS

Adult and pediatric patients who had nonselective unilateral laryngeal reinnervation (ULR) surgery were prospectively enrolled from 1998 to 2016 in a tertiary university hospital center through an ethically approved trial (trial number: 97/059; North West Personnel Protection Committee I).

Patients with follow-up of at least 1 year were included in this analysis. Follow-up is still ongoing, but after 36 months there is a significant reduction in the amount of data collected due to loss of follow-up. This analysis therefore focuses on the first 36 months after ULR. Patients acted as their own control.

Pre- and Postoperative Assessment

Videostroboscopy was performed in all patients for verification of unilateral vocal cord paralysis. All examinations were conducted by senior laryngologists. The exams were performed using a XION (Berlin, Germany) videolaryngoscopy system.

Preoperative and postoperative evaluation included LEMG of the thyroarytenoid (TA) and the posterior cricoarytenoid muscles, verifying abnormal electrical activity. Spirometry was performed preoperatively and 1 year after surgery. Cervical/ thoracic computed tomography imaging was routinely performed preoperatively to exclude possible further causes for nerve injury. Voice quality assessments were carried out using voice self-evaluation questionnaires. The Voice Handicap Index (VHI)-10 and a questionnaire developed at our hospital—the Rouen Voice Questionnaire (RVQ)—were used. The RVQ is a voice self-evaluation questionnaire comprising 10 questions in addition to a linear self-evaluation with 140 possible points in total, 0 points being a normal voice. For comparison with the standardized VHI-10, a prediction model calculating corresponding VHI-10 values to specific RVQ values was calculated (Fig. 1).

A team of two phoniatric specialists performed objective voice assessment using the Hirano Voice Scale. The patient's voice was recorded into an individual sound file and labeled anonymously using Audacity (open-source digital audio editor for Windows (The Audacity Team, version 1- 2.3.1). Blinded assessment measurements by questionnaire and objective evaluation took place preoperative, 1 to 3 months, 6 months, 12 months, 24 months, and 36 months after surgery. Acoustic voice analysis including jitter, shimmer, maximal phonation time (s), and maximal phonation intensity (in decibels) was measured using the software PRAAT (version 5.1.03; University of Amsterdam, Amsterdam the Netherlands). These measurements took place preoperatively and 1 to 3 months, 6 months, and 12 months after surgery.

Indications for Surgery

The following conditions were considered indications for surgery:

- Permanent damage with proven neurotmesis on LEMG, either due to iatrogenic or idiopathic cause
- Dysphonia with breathy voice or diplophonia due to lack of adduction of the vocal cord, vocal cord bowing, vocal cord atrophy, or all three
- Requirement of optimal voice result due to professional usage of voice or strong personal preference
- Failure of conservative treatment in the form of speech therapy for more than 6 months leading to unsatisfactory recovery of voice quality or no change of electrophysiologic activity

Surgical Method: Ansa Cervicalis-to-RLN Anastomosis

In all cases the ansa cervicalis-to-RLN anastomosis technique and vocal cord augmentation of the paralytic side using autologous material (fat) were performed at the same time. A lateral incision is made in a skin crease at about the level of the lower edge of the cricoid cartilage. The platysma muscle is then incised, followed by careful dissection of the sternocleidomastoid muscle fascia, paying close attention to the ansa cervicalis. The ansa cervicalis can usually be found crossing the jugular vein. It can also be located by careful examination of the posterior aspect of the omohyoid or sternohyoid muscles. Once identified, the ansa cervicalis is dissected proximally to the lateral edge of the jugular vein and distally into the strap muscles. Electrical stimulation of the nerve can be performed for confirmation. No specific branch is chosen.

Next the RLN is identified. If the cervical region is intact, for example due to a thoracic lesion of the RLN, the RLN can be identified inferior to the thyroid gland and dissected in a cranial direction. More frequently in cases of cervical injury, a retrograde dissection can be performed. A single hook is placed around the posterior part of the thyroid cartilage, permitting its rotation. The RLN is found underneath the inferior pharyngeal constrictor muscle, which must be sectioned, behind the cricothyroid joint entering the larynx. Usually, the scar tissue does not extend behind the cricopharyngeal muscle. The RLN trunk is then dissected several centimeters inferiorly. Before either nerve is divided, it is necessary to verify that there is enough length to allow a tension-free

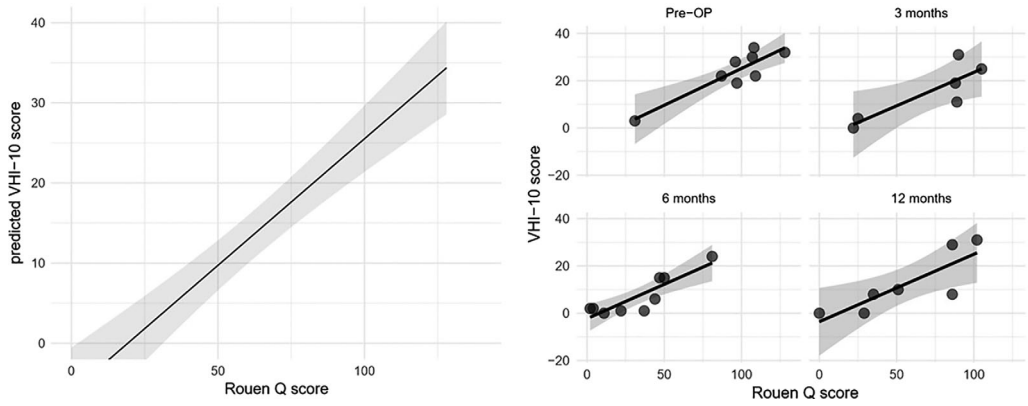

Fig. 1. Regression analysis model Rouen Voice Questionnaire/VHI-10. VHI = Voice Handicap Index.

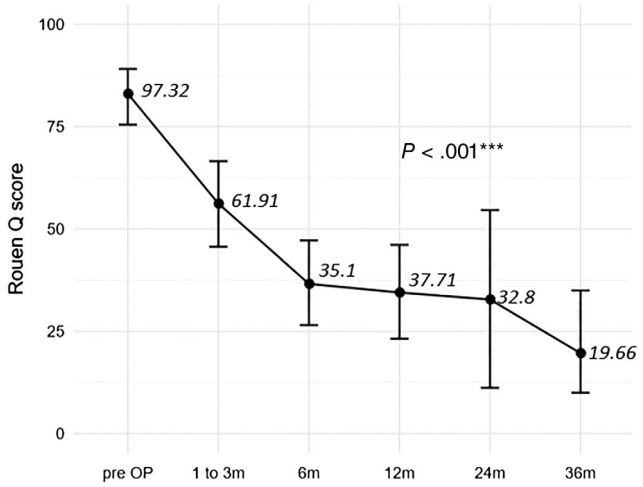

Fig. 2. Voice questionnaire (Rouen Voice Questionnaire): development over time points.

anastomosis anticipating larynx movement during swallowing. A branch of the ansa cervicalis is cut at the point where the diameter is similar to that of the RLN. After sectioning of the nerves, the cut ends are prepared by resection of axonal excess, whereas the epineurium is preserved. End-to-end anastomosis is performed using standard microsurgical techniques under magnification. Epi-perineural anastomosis is performed using two to six sutures by monofilament nonresorbable 9/0 thread; biological glue can be used but is not necessary. Closure is conventional, in two layers, with drainage. No antibiotic-prophylaxis. Oral diet was allowed on the following day.

Vocal Cord Augmentation

In addition to ansa cervicalis-to-RLN anastomosis, all patients underwent augmentation of the paralyzed vocal cord, if not previously done in the salvage situations, at the time of reinnervation surgery. Fat was harvested and prepared as described elsewhere[9] and injected into the deep portion of the TA and laterally regarding the vocal process.

Statistical Analysis

Data were entered in an Excel 2011 (Microsoft, Redmond, WA) spreadsheet and analyzed in R statistical software (The R Foundation for Statistical Computing, Vienna Austria).[10] Descriptive statistics were used to document the change of digital phonation values, voice grading values, and voice assessment questionnaire values over time.

To assess predicted linear improvements over time, data were submitted to linear mixed-effects models.[11] These models allow testing for polynomial trends (e.g., linear, quadratic) while explicitly modeling the within-subject dependency of longitudinal measurements through subject-specific random components and correctly adjusting estimates with missing values. Missing values were due to loss to clinical follow-up. *P* values were derived using the Satterthwaite approximation.[12]

Results were declared significant improvements over time when a dependent variable's estimated slope parameter had the predicted sign (depending on the measured variable) and when it was shown to be significantly different from zero with $P < .05$.

RESULTS

ULR All Patients

Forty-eight patients were enrolled and treated with the ansa cervicalis-to-RLN anastomosis technique. The causes of UVFP were cancer involving the RLN (27.1%, 13/48), iatrogenic nerve transection (60.4%, 29/48), and idiopathic (12.5%, 6/48). Localization of the site of nerve injury where possible was intracranial/skull base in three cases, cervical along the vagus nerve in seven cases, thoracic in 15 cases, cervical in the region of the thyroid in 17 cases, and unknown in six

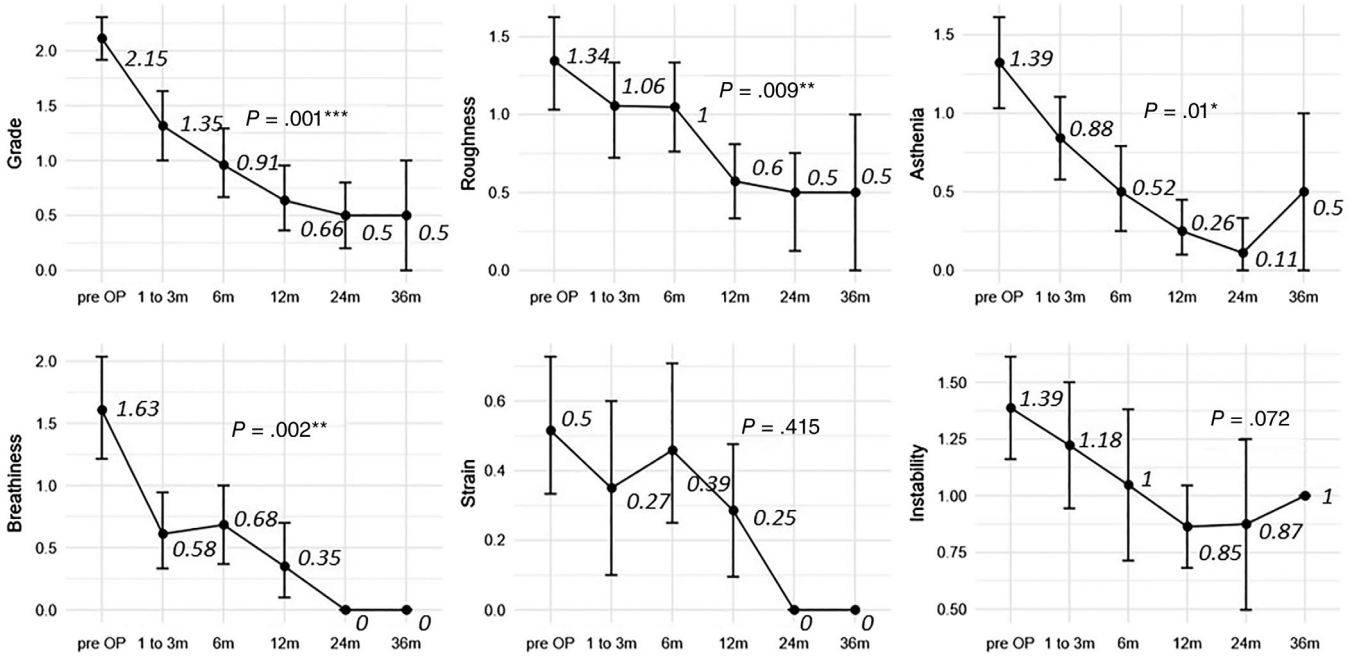

Fig. 3. Hirano voice score: development over time points.

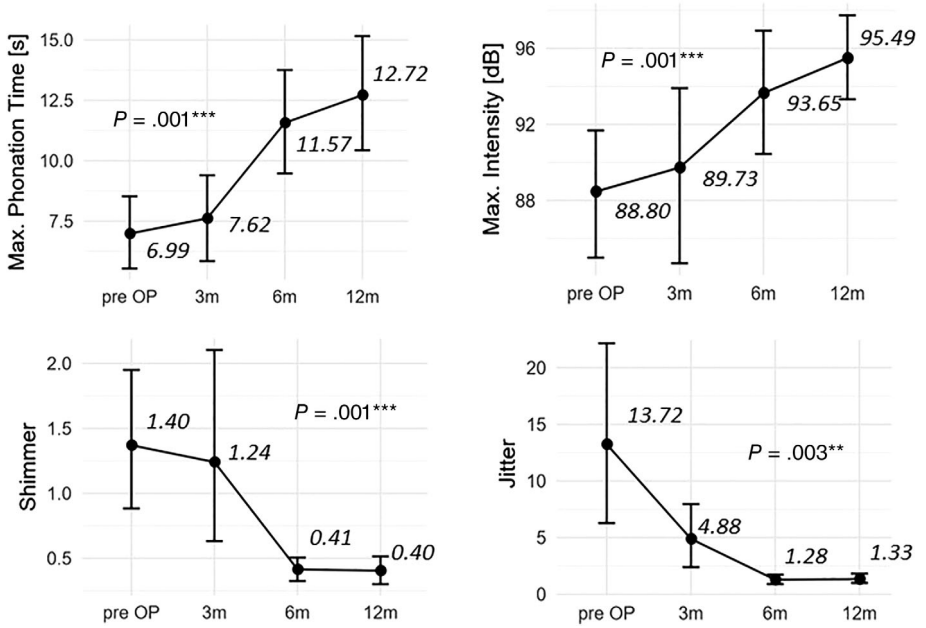

Fig. 4. Digital phonation analysis: development over time points.

cases. Mean patient age at the time of ULR was 50.56 years, the median being 54 years. The youngest patient was 2 years old, and the oldest patient was 74 years old at time of surgery. The time between probable laryngeal recurrent nerve trauma and ULR ranged between 1 and 40 years, the median being 5.77 years.

RVQ/VHI-10 questionnaire. Significant linear improvement of self-evaluation of voice quality over time was measured ($P < .001$) (Fig. 2). Values in brackets are comparative VHI-10 values resulting from a prediction model calculating corresponding VHI-10 values to specific RVQ values (Fig. 1).

Hirano score. Significant linear improvement of externally assessed voice quality was observed in grade ($P < .001$), breathiness ($P < .002$), roughness ($P < .009$), and asthenia ($P < .01$).[13] No significant linear improvement over time was measured in strain ($P < .415$) and instability ($P < .072$). Development of GRBASI parameters (Grade, Roughness, Breathiness, Asthenia, Strain, Instability) is shown in Figure 3.

Significant linear improvement over time of maximal phonation time ($P < .001$), maximal phonation intensity ($P < .001$), jitter ($P < .003$), and shimmer ($P < .001$) could be observed. Development of digital phonation parameters over time is shown in Figure 4. The aerodynamic consequences of ULR were also studied. Mean forced inspiratory volume in 1 second (FIV_1) decreased slightly from 2.74 (L/sec) preoperatively to 2.2 (L/sec) after ULR. LEMG enrichment was observed in the TA muscles when systematically recorded 1 year after reinnervation.

ULR as Salvage Treatment

Eight of the 48 patients underwent reinnervation as a secondary approach after previous thyroplasty or vocal cord augmentation had not proven to be sufficient and no improvement of voice quality was demonstrated. Data of the salvage patients were also included in the nonsalvage ULR group. Initial localization of injury to the ULR nerve in these cases was thoracic in two cases, cervical in five cases, and nondistinguishable in one case. The mean patient age at time of ULR was 41.87 years, the median being 54 years. The youngest patient was 7 years old, and the oldest was 65 years old at time of operation. Time between probable laryngeal recurrent nerve trauma and ULR ranged between 3 and 7 years, the median being 5.8 years. Primary therapy was augmentation with fat in five, augmentation with calcium hydroxylapatite in one case, and thyroplasty with Montgomery prosthesis in two cases.

Results are presented as for primary ULR group.

Questionnaire RVQ/VHI-10. Significant linear improvement of self-evaluation of voice quality was measured ($P < .001$) (Fig. 5).

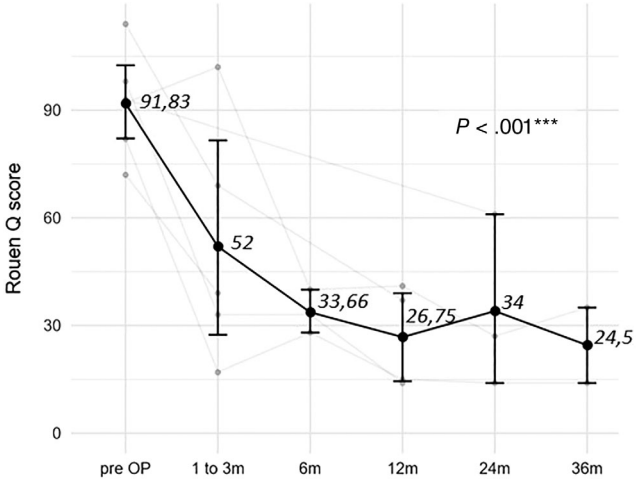

Fig. 5. Voice questionnaire (Rouen Voice Questionnaire) of the salvage group: development over time points.

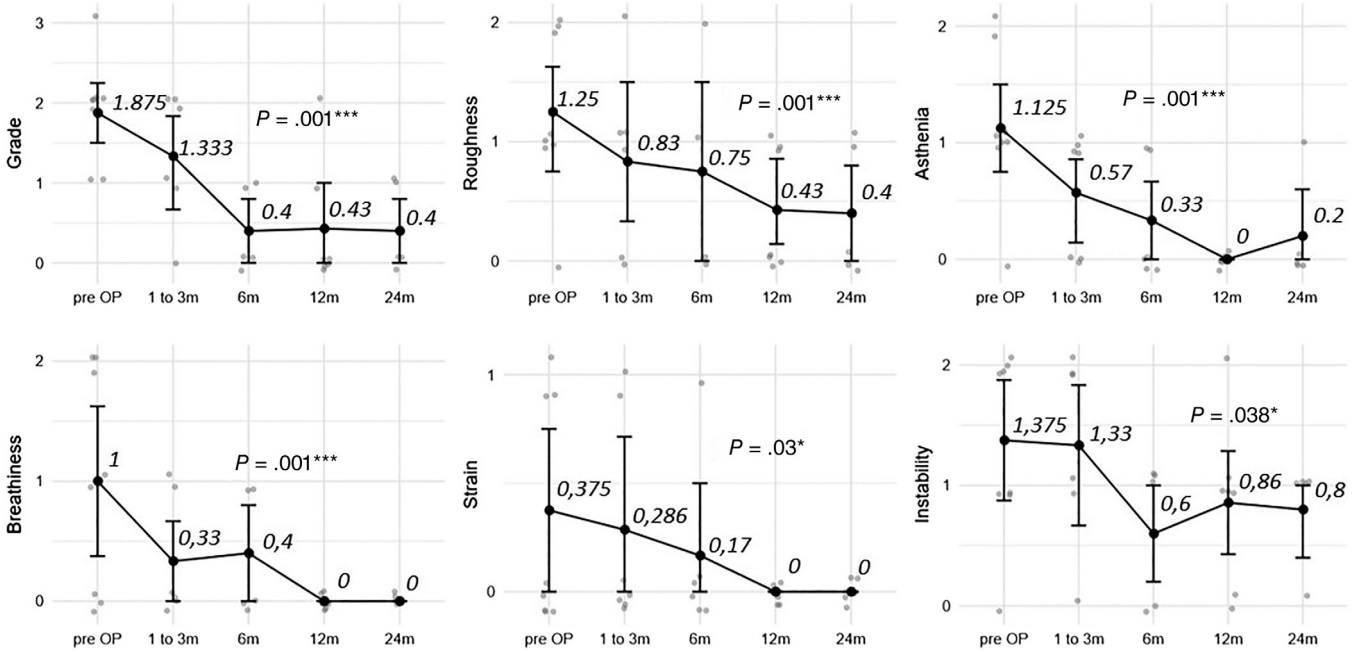

Fig. 6. Hirano voice score of the salvage group: development over time points.

Hirano score (GRBASI). Significant linear improvement of externally assessed voice quality was observed in grade ($P < .001$), roughness ($P < .001$), breathiness ($P < .001$), asthenia ($P < .001$), strain ($P < .03$), and instability ($P < .038$). Development of GRBASI parameters for salvage ULR over time is shown in Figure 6.

Significant linear improvement maximal phonation intensity ($P < .012$), jitter ($P < .01$), and shimmer ($P < .017$) could be observed. No significant linear improvement for of maximal phonation time ($P < .065$) was observed (Fig. 7).

A comparison of development of voice parameters after ULR in salvage and nonsalvage group showed no significant difference between both groups as visualized for the Hirano voice scores in Figure 8. Mean FIV_1 measured in patients through spirometry decreased slightly from 2.31 L/sec preoperatively to 2.22 L/sec after ULR (not significant).

VHI-10 results of recall patients were as follows (values in parentheses are comparative RVQ values resulting from the above-described prediction model):

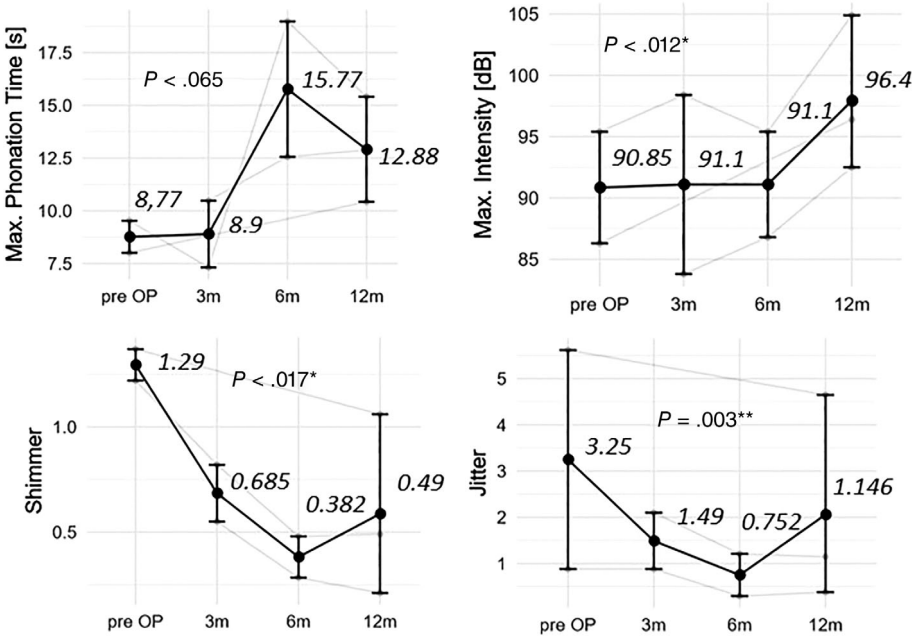

Fig. 7. Digital phonation analysis of the salvage group: development over time points.

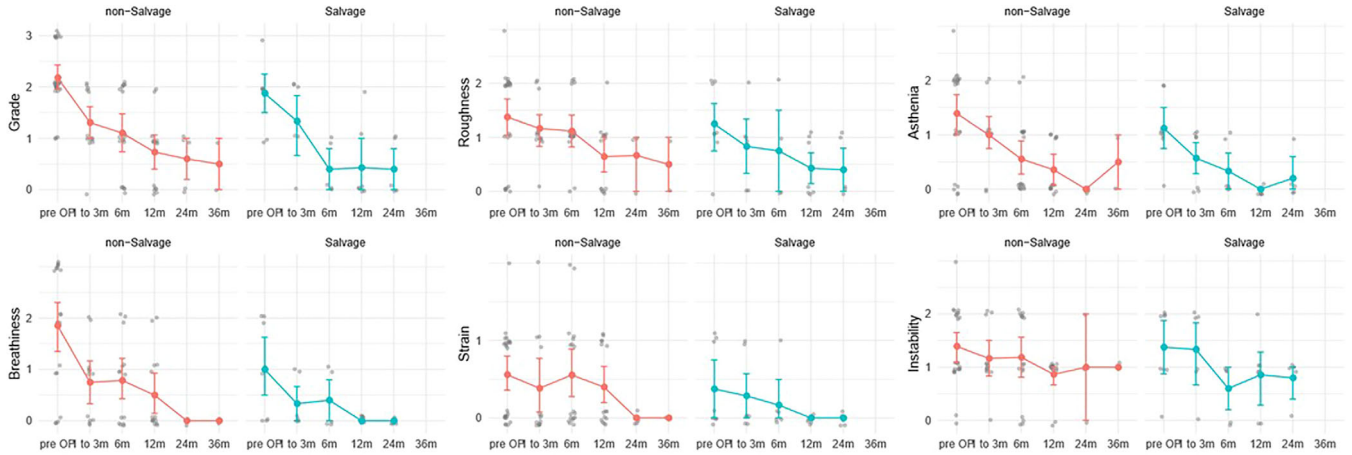

Fig. 8. Comparison of the Hirano voice score for the unilateral laryngeal reinnervation (ULR) primary group and Hirano voice score ULR salvage group. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

patient 1: 2 (~25), 12 years after ULR; patient 2: 10 (~50), 11 years after ULR; patient 3: 9 (~45), 6 years after ULR; patient 4: 7 (~40), 4 years after ULR; and patient 5: 16 (~70), 5 years after ULR. Recall results were excluded from statistical analysis due to lack of comparability with follow-up time points.

DISCUSSION

To demonstrate voice improvement due to axonal regrowth we included 48 patients over the course of 18 years. Our results indicate an improvement of voice quality over time after ULR. Follow-up intervals were set closely together shortly after ULR as we discovered the effect of axonal growth to occur between months 4 and 6. Intervals were then set farther apart to monitor stability of quality of voice over time. The first voice improvement was recorded directly after surgery, which we attribute to vocal cord injection. Further improvement of voice quality occurred mainly 3 to 6 months after ULR, and voice quality remained stable over time or improved further. We attributed this voice improvement over time to the stability of the arytenoid obtained by global reinnervation of all the muscles of the previously paralyzed hemi-larynx. The resulting effect is similar to type I synkinesis.[14] We compare the effect of all muscles contracting and hence pulling on the arytenoid to that of the springs of a trampoline on the center surface. This results in the recovery of viscoelasticity of the vocal fold and the repositioning of the vocal fold in a similar position as that of the opposing side, leading to improvement of the wave phenomenon, which is vocal fold vibration.[15] We consider a general voice improvement, LEMG enrichment in the TA muscles, and long-term voice stability following ULR as strong arguments in favor of our primary objective of demonstrating improvement and the long-term stability of the voice following nonselective reinnervation. We also consider significant additional voice improvement 3 to 6 months after surgery, surpassing the initial effect of augmentation, to support our secondary objective of demonstrating voice improvement attributable to axonal regrowth.

At first, our study was designed as a prospective comparative study comparing unilateral reinnervation in cases of severe denervation proven by electromyography and thyroplasty performed under local anesthesia. When it became apparent that voice results were better for patients treated with reinnervation, thyroplasty was canceled, and only reinnervation was continued from 1998 until 2016.

When compared to conventional vocal cord medialization thyroplasty, we presume that the ability of the reinnervated vocal fold to freely vibrate plays an important role in high voice quality after reinnervation when compared to the more static condition after thyroplasty as also suggested elsewhere.[16] We attribute the long-term stability of voice quality to restoration and preservation of laryngeal muscle innervation preventing muscular atrophy. To further affirm our experience concerning better voice results after ULR than after thyroplasty, a direct comparison study needs to be implemented as suggested by Blackshaw et al.[17]

We are aware that the extent of improvement of voice quality in our patients due to ULR cannot clearly be differentiated from the effects of vocal cord augmentation, which was implemented at the same time. Most authors, however, agree that the effect of vocal cord augmentation is not permanent and lasts approximately 6 months (Restylane), 12 months (fat), and 18 months (calcium hydroxyapatite).[2,18–20] Our results indicate both stability and further improvement of voice quality over time. We therefore argue that this is due to reinnervation. Our results are in accordance to Paniello et al., who demonstrated a significant improvement in voice quality in the ULR group 6 to 12 months after surgery.[16]

The exact time of onset of voice improvement due to reinnervation is difficult to determine, as vocal cord augmentation and ULR were performed at the same time, and LEMG was not performed until 12 months after surgery. Our data show further improvement of voice quality between 3 months and 6 months; therefore, we believe the effect of reinnervation appeared during this time.

Wang et al. describe a significant voice improvement after ULR in patients who suffered UVFP after thyroid surgery.[21] A comparison of development of voice quality over time with our group is not possible, as the authors do

not differentiate results between postoperative time intervals. Paniello et al. describe a significant increase of voice quality during the 6 to 12 months period after ULR in a collective of patients under the age of 52.[16] These findings are in accordance with our results indicating the effect of synkinetic reinnervation beginning 3 to 6 months after surgery.

Some of our patients had RLN resection close to the larynx due to cancer. By retrograde dissection of the RLN close to the cricopharyngeal muscle, the RLN was always found, even in severely scarred tissue. We therefore encourage ULR also in patients where cervical surgery was previously performed.

The mean time between probable RLN injury and reinnervation in our patient series was 5.7 years. Our data indicate that delay between injury and ULR does not hamper axonal regrowth and hence voice improvement due to reinnervation. A case with a delay of 23 years between probable nerve injury and ULR improved from a VHI-10 score of 22 before surgery to a score of 15 at 6 months and a score of 8 at 12 months after surgery.

We observed a slight postoperative decrease on inspiratory volume after 1 year. This may be explained as a side effect of passive medialization due to decrease of the glottis surface because of augmentation and decreased vocal cord bowing due to reinnervation. This effect on the glottis shape with aerodynamic consequences is probably the same as in endoscopic augmentation, external medialization, or arytenoid adduction. This effect must be taken into consideration if this procedure is to be performed on athletes. In this case, selective reinnervation may be preferable or discussed.

The salvage group was done (composed) with patients having previously received either vocal fold augmentation or thyroplasty. As in primary ULR, significant improvement of voice was seen in salvage ULR in all assessed voice quality parameters. Voice results remained stable for up to 12 years, confirmed via questionnaires sent to patients. Hence, we strongly propose nonselective ULR to be considered as salvage treatment for patients on whom conventional voice surgery has failed.

Our patient cohort also included several children with UVFP. In all cases, significant improvement of voice was achieved and maintained. We are therefore in accordance with Zur et al.[22–24] and Smith et al.[25,26] in strongly suggesting ULR as a primary treatment option for children and adolescents with UVFP due to the longevity of its effect and nondependency on anatomical changes of the larynx associated with growth.[27]

We understand there may be concerns about why it took a significant amount of time to recruit a small number of patients. The reason is that nonselective reinnervation is indicated in patients who have no aspiration as the first clinical sign, have a long provisional outcome, which is not the case in all the lung cancer patients, and who need a high quality voice (e.g., voice professionals). Moreover, the indication is accepted in patients who have a strong electrophysiologically proven denervation, to ensure that patients do not have worse outcomes than what they would have with spontaneous recovery. These strict criteria reduce the number of eligible patients.

Our personal experience further indicates that nonselective reinnervation can reduce dyspnea associated with UVFP, by decreasing arytenoid invagination during inspiration. It can also reduce aspiration in children with UVFP by increasing the force of glottic closure.[23]

CONCLUSION

Nonselective ULR in unilateral vocal cord paralysis is a reliable and stable therapeutic option for patients with high expectations concerning voice quality. The effect is stable in long-term results. It does not preclude growth, as it is not dependent on rigidity or quantity of implanted materials and is therefore an excellent option in children.[25] It is also a viable option for patients in whom conventional voice surgery failed to improve voice quality. We therefore also propose ULR as salvage option in UVFP.

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