可恢復性聲帶麻痺的自然病史：神經再支配動力學的啟示

The Natural History of Recoverable Vocal Fold Paralysis: Implications for Kinetics of Reinnervation

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Commentary

我們常告知單側聲帶麻痺 (unilateral vocal fold paralysis) 的病人需要 12 個月的時間來自然康復。德州大學西南醫學中心以病例系列研究合併從頭開始的數學建模來發展神經生理擬真的恢復模型，並使用該模型來產生有意義的預測。研究團隊回溯研究 7 年內 727 例單側聲帶麻痺，發現有 44 位自然恢復且其嗓音的開始改善是分離不連續的。模型的假設在於早期恢復組肇因於神經受傷 (neuropraxia)，而晚期恢復組是因為更嚴重的神經損傷，而早期組的恢復可用 2 階段模型來解釋恢復的時間的不同：第一階段，再生的軸突必須越過損傷的區域 (可能期)，第二階段，神經不受阻礙的在喉部生長 (決定期)。一種混合分佈包括兩個階段 (指數性改良式高斯分布) 可以準確地建立恢復時間的模型 ($R^2=0.918$)。這種模型可預測 86% 可恢復性聲帶麻痺患者在 6 個月內恢復嗓音，96% 在 9 個月內恢復。而早期的嗓音恢復與聲帶運動恢復和較年輕的年紀有關。本研究的發現指出，目前的等待 12 個月來自然康復或許太保守了。與其他周邊神經再生的研究相似，需修復跨越損傷部位的神經，和神經不再生長到喉部，或許是神經再生的速率決定步驟。同我們已知的概念，神經受傷的越嚴重，喉返神經就越難再生或需花更久的時間越過受傷的區域抵達喉部；因此，第一階段所需的時間需要越長。第二階段受到喉返神經再生需穿越的長度和神經再生的速度，而神經再生速度將受病人年齡所影響。事實上，年齡對第一階段的影響可能更大，比第二階段還高。因此，本研究認為嗓音恢復時間的變異性受到修補原來受傷的位置或越過第一階段的差異性所影響。

根據這一個模型，如果估算 9 個月內恢復的機會不到 5%，我們應合理的使用長期性的介入治療，如內推式喉成型術 (medialization laryngoplasty)、杓狀軟骨復位術 (arytenoid reposition)、或聲帶注射效果較長的材質來改善病人的嗓音。而如果恢復的機會推估不到 1%，則可以考慮等待 12 個月，若未再生，則進行 ansa-RLN 神經移植術。

本研究的限制包括：喉肌電圖不一定能展現神經再生，及樣本數需要再大一點。然而，根據這一個研究，我們可以做一個較精準的神經再生判斷，而提供給臨床醫師作為介入的時間點與介入方式的參考。

關鍵詞：喉返神經再支配，喉返神經，周邊神經再生，聲帶麻痺，類高斯
The Natural History of Recoverable Vocal Fold Paralysis: Implications for Kinetics of Reinnervation

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Objectives/Hypothesis: Patients with unilateral vocal fold paralysis (UVFP) are commonly told to wait 12 months for spontaneous recovery. This study aims to 1) determine the time to vocal recovery in UVFP, 2) use that data to develop a neurophysiologically plausible model for recovery, and 3) use the model to generate meaningful predictions for patient counseling.

Study Design: Case series with de novo mathematical modeling.

Methods: Patients with UVFP who could pinpoint a discrete onset of vocal improvement were identified. The time-to-recovery data were modeled by assuming an “early” recovery group with neuropraxia and a “late” recovery group with more severe nerve injury. For the late group, a two-stage model was developed to explain the time to recovery: regenerating axons must cross the site of injury in stage 1 (probabilistic), followed by unimpeded regrowth to the larynx in stage 2 (deterministic).

Results: Of 727 cases of UVFP over a 7-year period, 44 reported spontaneous recovery with a discrete onset of vocal improvement. A hybrid distribution incorporating the two stages (exponentially modified Gaussian) accurately modeled the time-to-recovery data ($R^2 = 0.918$). The model predicts 86% of patients with recoverable UVFP will recover within 6 months, with 96% recovering within 9 months. Earlier vocal recovery is associated with recovery of vocal fold motion and younger age.

Conclusions: Waiting 12 months for spontaneous recovery is probably too conservative. Repair across the site of injury, and not regrowth to larynx, is likely the rate-determining step in reinnervation, consistent with other works on peripheral nerve regeneration.

Key Words: Laryngeal reinnervation, recurrent laryngeal nerve, peripheral nerve regeneration, vocal fold paralysis, exponentially modified Gaussian.

Level of Evidence: 4.

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INTRODUCTION

The uncertainty of recovery from a new diagnosis of unilateral vocal fold paralysis (UVFP) can be distressing to patients and is often a salient topic of discussion with the physician. The prevailing notion holds that 12 months should elapse to allow for possible spontaneous recovery before definitive intervention is pursued.$^1$ The wait time of 12 months appears to derive from convention rather than evidence. There is a dearth of data on the natural course of vocal recovery from UVFP. In fact, a literature review of the natural history of idiopathic UVFP revealed that most cases appeared to recover in well under 12 months.$^2$ There is therefore a real possibility that the 12-month waiting period results in delayed treatment and unnecessary negative impact on quality of life.$^3,4$ More data on the natural course of spontaneous recovery are needed.

It is well-established that vocal recovery from UVFP can occur without the recovery of normal vocal fold (VF) motion due to synkinetic reinnervation.$^5$ Various studies report 13% to 32% of patients recover voice without recovery of VF motion.$^6,8$ Recovery of voice, whether through normal or synkinetic reinnervation, provides a functional marker for the underlying process of nerve regeneration. It has been our observation and that of others that for some patients the vocal recovery is gradual, but others experience a more abrupt onset of voice improvement that can be pinpointed to within a week or two.$^2$ A similarly discrete onset of voice improvement is also noted by patients who undergo ansa cervicalis-recurrent laryngeal nerve (RLN) reinnervation, many of whom report a transition of around 3 months postoperatively.$^{10-13}$ In either case, the sudden vocal improvement likely reflects a sufficient number of regenerating axons simultaneously reaching the laryngeal adductors to produce a noticeable gain in vocal function. The time from the onset of voice loss to the onset of voice improvement therefore can be regarded as a surrogate marker for the kinetics of RLN regeneration.

The goal of this study was to develop a probabilistic approach for the time to vocal recovery that is more practical for patient counseling than arbitrary time points. The general hypothesis was that the time to vocal recovery can be modeled based on simple assumptions of how...
the RLN regenerates following injury. A specific hypothesis was that vocal recovery follows a bimodal temporal distribution that reflects an early group with neuropraxia and a late group with more severe nerve damage. Our three specific aims were 1) to determine the time to vocal recovery in a cohort of patients with UVFP, 2) to use that data to develop a neurophysiologically plausible model for RLN regeneration, and 3) to use the model to generate meaningful predictions for patient counseling regarding the time to vocal recovery.

MATERIALS AND METHODS
Subjects and Data Collection
The study protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center. A prospective clinical database was reviewed to identify all patients with a primary diagnosis of UVFP seen between 2008 and 2015. The time of onset of voice improvement was documented at the visit immediately after the voice started to improve, typically within a few weeks of the actual onset. The motion status of the affected VF reflects the consensus of two laryngologists who retrospectively reviewed the videolaryngo-scoptic exams to classify each VF as either immobile or showing purposeful motion, defined as the presence of active abduction with sniff or inspiration.

Conceptual Framework for Modeling
Spontaneous recovery from VF paralysis was assumed to take place in an “early” recovery group that sustained neuropraxia, versus a “late” recovery group with axonal disruption. The late group would encompass axonotmesis and neurotmesis. Time to vocal recovery in the early group was modeled as a normal (Gaussian) distribution (Fig. 1A). The following conceptual framework was proposed for reinnervation in the late group.

1. Reinnervation takes place in two stages. The first stage entails the regenerating axons crossing the site of injury to reach the uninjured, distal stump containing the empty neurolemma tubes (Fig. 1B). (In this article, the distal stump is broadly taken to mean the most proximal endpoint of the distal RLN segment that still contains intact neurolemma tubes. In a nonseverance injury [e.g., stretch], there would not be a physical distal stump, but a functional distal stump is still present.) This stage is a hurdle the reinnervating axons must clear. The second stage entails unimpeded regeneration through the distal nerve segment to reach the intrinsic laryngeal muscles (Fig. 1C).

2. The first stage is probabilistic. The more axons that are able to sprout proximal to the site of injury, the more likely some will reach the distal stump. The more severe the injury, the less likely the proximal axons can bridge the gap and reach the distal stump. This stage is heterogeneous in nature, because the mechanism of injury is variable (e.g., by stretch, crush, thermal, or mechanical severance). There may also be varying lengths of retrograde degeneration that regenerating axons need to make up before even reaching the site of injury.34 In the end, whether this stage is traversed becomes a matter of probability. The time to traverse this stage can be modeled as an exponential delay function (Fig. 1B). An injury with high probability of recovery (e.g., large number of surviving axons, low-grade injury) would traverse the site of injury earlier, and an injury with low probability of recovery (e.g., fewer number of surviving axons, more severe injury) would traverse later, if ever.

3. The second stage is deterministic. Once regenerating axons succeed in crossing the site of injury and reaching the distal stump, it is virtually certain that the larynx will be

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Fig. 1. Schematic of early and late recovery groups with associated probability distributions. A single neuron is shown for simplicity, with the understanding that the recurrent laryngeal nerve is made up of multiple axons. (A) Early recovery group corresponds to neuropraxia, or a conduction block. The time to recovery is modeled by a simple Gaussian. (B) Late recovery group corresponds to axonal disruption. Stage 1 involves regeneration across the site of injury. This probabilistic stage is modeled as a decaying exponential. (C) Stage 2 involves axonal regrowth from the end of stage 1 to the larynx. This deterministic stage is modeled as a Gaussian. (D) Late group as an exponentially modified Gaussian. (E) Combined cohort. Graph axes: p = probability, t = time. Illustration by Lisa A. Clark, MA, CMI.
reinnervated after some amount of time. There may be slight individual variation in how fast the axons grow and in the length of the distal segment to traverse. This variation can be modeled as a normal (Gaussian) distribution (Fig. 1C).

**Mathematical Modeling and Data Fitting**

Modeling and data fitting were performed based on the method of Lacouture and Cousineau as detailed in the Supporting Information, Appendix, in the online version of this article.

**Statistical Analysis**

The goodness of fit of the overall model to the raw data is intrinsic to the maximum likelihood estimation fitting approach (see Supporting Information, Appendix, in the online version of this article), in that a goodness-of-fit criterion, the likelihood value LogL, is maximized. As a second criterion, the $R^2$ measure of goodness of fit was computed between the model and a 20-bin histogram of the data, using a custom routine in MATLAB (The MathWorks Inc., Natick, MA). For the relationship between time to vocal recovery versus return of motion or age, the $\chi^2$ test was performed with SAS 9.3 (SAS Institute Inc., Cary, NC) with two tails and level of significance set at $P = .05$.

**RESULTS**

Of 727 cases of UVFP over a 7-year period, 96 patients experienced spontaneous recovery of voice, of which 44 could identify a discrete point in time at which their voice suddenly improved. Twenty-four (55%) were women and 20 (45%) were men. The average age was 55.9 years (median, 57.0 years; range, 22–83 years).

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Thyroid/parathyroid</td>
<td>8 (18.2)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>7 (15.9)</td>
</tr>
<tr>
<td>Spine</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Esophageal</td>
<td>2 (4.5)</td>
</tr>
<tr>
<td>Carotid</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td><strong>Surgery subtotal</strong></td>
<td><strong>22 (50.0)</strong></td>
</tr>
<tr>
<td>Intubation</td>
<td>8 (18.2)</td>
</tr>
<tr>
<td>LMA</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Neck abscess</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Idiopathic/postviral</td>
<td>12 (27.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44 (100)</strong></td>
</tr>
</tbody>
</table>

LMA = laryngeal mask airway; UVFP = unilateral vocal fold paralysis.

The time to vocal recovery ranged from 2 to 52 weeks (median, 13.9 weeks; mean, 15.6 ± 11.0 weeks) and did not follow a normal distribution. The data are shown as a histogram in Figure 2, with the model probability distribution superimposed ($R^2 = 0.918$). Model parameters are listed in Table A1 in the Supporting Information, Appendix, in the online version of this article. Based on the model, the cumulative probability of vocal recovery at select time points are tabulated in Table II.

![Fig. 2. Time to vocal recovery (histogram). The probability distribution as modeled by the process detailed in the Appendix in the online version of this article and schematized in Figure 1 is shown as a solid line superimposed on the histogram.](image)

![Fig. 3. Recovery of vocal fold motion. The histogram shows time to vocal recovery as in Figure 2. Patients with recovery of vocal fold motion are in light gray. Those without vocal fold motion recovery at the most recent follow-up are in black.](image)

<table>
<thead>
<tr>
<th>Months</th>
<th>Probability</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>65.9 %</td>
</tr>
<tr>
<td>6</td>
<td>85.6 %</td>
</tr>
<tr>
<td>9</td>
<td>96.0 %</td>
</tr>
<tr>
<td>12</td>
<td>98.9 %</td>
</tr>
<tr>
<td>18</td>
<td>99.9 %</td>
</tr>
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Of the 44 patients who experienced discrete onset of vocal recovery, 31 (70%) demonstrated some degree of return of VF motion at their last clinic follow-up, whereas 13 (30%) still had an immobile VF. However, nine of the 13 patients in the latter group had follow-up less than 6 months, so the 70% figure likely underestimates the eventual recovery of VF motion. Return of VF motion is more common in patients who had an earlier onset of vocal recovery than later (Fig. 3). When the data were dichotomized based on the median time to vocal recovery of 14 weeks, those who recovered sooner than 14 weeks were more likely to have return of motion (P = .003).

The relationship between age and time to vocal recovery was tested by dichotomizing the data based on the median age of 57 years. Patients aged 57 years and over tended to recover later than those under 57 years (P = .015).

**DISCUSSION**

A relatively simple model for the time to vocal recovery following RLN injury is proposed. The model is neuro-physiologically plausible, and its predictions are consistent with existing data. Most importantly, it provides a probability distribution that can be used to counsel patients with a new diagnosis of UVFP with regard to the wait time for spontaneous recovery. Probability-based patient education in UVFP has been focused on the likelihood of eventual recovery based on laryngeal electromyography (LEMG). The current work does not pertain to the likelihood of recovery per se. Rather, it only concerns the timing for those who will eventually recover their voice. It provides a framework for decision making based on probabilities rather than arbitrary wait times.

**Predictions of the Model Are Consistent With Published Data**

Predictions of the model are consistent with a variety of clinical and laboratory data. The recovery peak at 11 to 13 weeks corresponds nicely to the typical report of significant voice improvement at 3 to 4 months following ansa-RLN reinnervation, as well as the 3-month mark at which reinnervation is noted in canine models of RLN denervation. Patients with UVFP who recover VF motion have been reported to do so after a mean of 4.6 to 5.0 months or a median of 5 months. Because vocal recovery would precede recovery of VF motion in many cases, we would consider that time frame consistent with our model. For the early group, optimal fitting of the time to recovery yielded a mean of 4.2 weeks and standard deviation of 1.4 weeks. It follows that 95% of the early group should recover within about 6 to 7 weeks, which is consistent with studies of synkinesis in a rat model. In a systematic review of idiopathic vocal fold paralysis, five cases out of 717 (0.7%) recovered beyond a year, which is consistent with the model prediction of approximately 1% recovering beyond 12 months. Rather than regarding these delayed recoverers as anomalies, they are simply the tail part of the same probability distribution describing the entire population of recoverers.

**Similar Models in Other Biological Processes**

The proposed two-stage framework for the late recovery group is rooted in literature on nerve regeneration and also parallels the kinetics of other biological processes. Holmquist et al. proposed a mathematical model for peripheral nerve regeneration following transection. The model incorporated an initial delay followed by a constant rate of regeneration. We have adopted this two-stage concept to equate the first stage with the initial delay and the second stage with subsequent regeneration. However, instead of a constant rate for the second stage, we use a Gaussian or normal distribution for the rate to account for clinical variance. Many biological variables distribute normally with a symmetric, bell-shaped curve (Gaussian) centered around a mean with symmetric spread according to a standard deviation. Combining the initial exponential decay with the Gaussian results in the exponentially modified Gaussian (ex-Gaussian) distribution, which has also been used to describe the variability of intermitotic time in cell division, as well as peak analysis in molecular chromatography and electrophoresis. These processes have in common a probabilistic component (modeled with exponential) and a deterministic component (modeled with Gaussian). The advantage of the ex-Gaussian over other common fitting functions is that its parameters can be interpreted in physiologically meaningful terms to provide insight into the underlying process.

**Model Implications**

The model suggests that the time to recovery in the late recovery group is largely determined by stage 1 (i.e., the likelihood of crossing the site of injury). The more severe the injury, the more difficult it would be and the longer it takes to cross the site of injury, so the total time for the regenerating axons to reach the larynx is lengthened by the time spent in stage 1. To put it another way, the exponential decay in stage 1 is responsible for the tail part of the probability distribution. Stage 1 can be thought of more broadly as the time it takes to repair the rate-limiting nerve deficit. In idiopathic VF paralysis, for example, even though a physical lesion may not be present, stage 1 would correspond to the time to overcome whatever conduction block needs to be overcome.

Stage 2 is deterministic in that once the regenerating axons complete stage 1, they are assured to complete stage 2. However, the time it takes to traverse stage 2 is variable. This variation could be due to two factors in principle: the length of RLN that needs to be traversed (i.e., between site of injury and the larynx) and the rate of nerve regeneration. For example, the length would be less in a shorter person with a short neck, and with a site of injury closer to the larynx. The impact of length is not known precisely, as Paniello et al. have shown that a difference of 5 cm did not translate into a substantial difference in time to electromyographic recovery in a canine model of RLN injury. The rate of regeneration is commonly assumed to be 1 mm/d, though Paniello et al. suggest this may not apply to the RLN. One possibility is that the rate may depend on the biological or chronological age of the patient.
In fact, age probably has a greater effect on stage 1 than stage 2. Age has been noted to be a factor in functional recovery from UVFP. Animal models of peripheral nerve regeneration have shown age to be an important predictor of outcome of nerve injury and repair. Older animals exhibit delayed myelin clearance and axon sprouting at the site of injury, reduced number and density of regenerating axons, lower specificity of regeneration, and greater fragmentation of the denervated neuromuscular junction. Importantly, the kinetics of functional recovery in Painter et al. suggest that the prominent effect of age is in a marked delay in the initiation of regeneration (corresponding to stage 1 in our model), rather than a slower rate of regeneration (corresponding to stage 2). Combining the age-related impaired regeneration from these animal experiments and the model from the current work, we would predict that older subjects make up more of the tail end of the distribution (dominated by the exponential decay in stage 1). This was borne out by a statistically significant association between age and the time of onset of vocal recovery. Finally, synthesizing the conclusions of Painter et al. (predominant effect of age is on stage 1), Holmquist et al. (initial delay is the main cause of variability), and the current work (the long tail is due to stage 1), we would conclude that most of the variability in time to vocal recovery is due to variability in repairing the initial site of injury or crossing stage 1.

Factors other than age and location of injury can also affect nerve regeneration quantity, quality, and rate. These include metabolic factors such as diabetes and nutritional status. This variability is modeled in the late group with the standard deviation parameter $\sigma_{\text{late}}$ (see Supporting Information, Appendix, in the online version of this article), which models the spread of the time to recovery due to these other factors.

**The Hypothesis of Bimodal Distribution**

There was substantial overlap between the early and late groups that one cannot simply infer the grade of injury (e.g., neuropraxia vs. axonal injury) from the time to vocal recovery. This overlap favors the concept that some cases of recoverable VF paralysis may actually involve a mix of neuropraxia and axonotmesis. A mixed injury mechanism is supported by laboratory studies. In a canine model where the RLN was stretched until compound motor action potentials were lost, some recovered motor unit potentials were seen as early as the first month, indicating that some axons were not traumatized by the stretch injury. If mixed injuries were produced in a carefully controlled laboratory setting, then it is likely that iatrogenic RLN injuries are even more heterogeneous in the clinical setting. In a single injury, some axons may be anatomically disrupted, whereas others in the same nerve may be demyelinated while maintaining structural integrity. This type of injury would fall in the overlap between the early group and the late group.

**Recommendations Based on Model**

The most important implication of this work for clinical practice is that the conventional wait time of 12 months for recovery should be reconsidered. By 9 months, with the probability of recovery less than 5%, it would be reasonable to pursue long-term interventions such as medialization laryngoplasty, arytenoid repositioning procedures, or injection with a long-lasting material. Any reinnervation that occurs later can only further improve the voice outcome. With regard to the timing of reinnervation procedures (e.g., ansa-RLN), most authors advise waiting at least 12 months. This appears reasonable according to the model, which predicts a 1% recovery rate after 12 months. Some authors advocate waiting as little as 6 months. However, about 15% of patients will recover beyond 6 months, which makes a procedure that removes any intrinsic reinnervation premature. For reinnervation procedures, the 12-months wait time appears appropriate.

**Limitations and Future Direction**

One limitation to this study was that reinnervation was not definitively demonstrated with LEMG. This was deliberate in the study design, because patients were unlikely to undertake the expense and discomfort of LEMG after they started to experience vocal improvement. We also did not feel LEMG was absolutely necessary, because favorable voice outcomes are correlated with electromyographic evidence of synkinetic innervation of the thyroarytenoid/lateral cricoarytenoid muscle complex in patients with persistently immobile, paralyzed VFs. Another limitation was that the parameter estimates could be more robust with a larger sample size. Efforts are underway for further data collection. Finally, 27% of the cohort had an idiopathic etiology. The two-stage model may not apply to this subset because it is unknown if there is a discrete site of dysfunction along the RLN. The degree of denervation based on quantitative LEMG is also less in idiopathic VFP compared to iatrogenic causes. Once the sample size of the idiopathic subset is sufficiently large, dedicated modeling of this group will be performed to see if the kinetics of recovery from idiopathic UVFP are distinguishable from iatrogenic UVFP.

**CONCLUSION**

This analysis provides the first evidence-based projection for the wait time for recoverable VF paralysis. The predictions agree with common clinical observations but provide a more accurate, probabilistic description of time to vocal recovery. The conventional advice of waiting 12 months for spontaneous recovery is likely too conservative and delays definitive treatment. The analysis also suggests that repair across the site of injury, and not the regrowth to the larynx, is the rate-determining step in reinnervation, consistent with other works on peripheral nerve regeneration.

**BIBLIOGRAPHY**
