



Current Treatment Options for Bilateral Vocal Fold Paralysis: A State-of-the-Art Review

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Vocal fold paralysis (VFP) refers to neurological causes of reduced or absent movement of one or both vocal folds. Bilateral VFP (BVFP) is characterized by inspiratory dyspnea due to narrowing of the airway at the glottic level with both vocal folds assuming a paramedian position. The primary objective of intervention for BVFP is to relieve patients' dyspnea. Common clinical options for management include tracheostomy, arytenoidectomy and cordotomy. Other options that have been used with varying success include reinnervation techniques and botulinum toxin (Botox) injections into the vocal fold adductors. More recently, research has focused on neuromodulation, laryngeal pacing, gene therapy, and stem cell therapy. These newer approaches have the potential advantage of avoiding damage to the voicing mechanism of the larynx with an added goal of restoring some physiologic movement of the affected vocal folds. However, clinical data are scarce for these new treatment options (i.e., reinnervation and pacing), so more investigative work is needed. These areas of research are expected to provide dramatic improvements in the treatment of BVFP.

Keywords. *Vocal Cord Paralysis; Synkinesis; Recurrent Laryngeal Nerve Injuries; Electric Stimulation Therapy; Botulinum Toxins*

INTRODUCTION

The term vocal fold paralysis (VFP) refers to the reduced or absent function of the vagus nerve or its distal branch, the recurrent laryngeal nerve (RLN) [1-3]. The most common causes include laryngeal or extralaryngeal cancers, iatrogenic injury during neck, thyroid gland, or chest surgery, and various neurogenic conditions (e.g., amyotrophic lateral sclerosis and closed head injury) [3-6]. The incidence of the bilateral VFP (BVFP) comprises about one third of all VFP cases [4]. Compared with unilateral VFP (UVFP), where normal ventilation can be relatively spared, the classical presentation of patients with BVFP is reduction of the glottal area resulting in various degrees of airway compromise. Patients will have noisy inspiratory breathing primarily with minimal voice change.

Acute bilateral VFP caused by iatrogenic nerve injury after

thyroid or other surgery can result in immediate symptoms in the recovery room requiring urgent airway intervention. In other cases, the airway symptoms can worsen over several weeks as a result of aberrant reinnervation or synkinesis. As the motor fibers in the RLN innervate both abductor and adductor muscles of the vocal fold, damage to the RLN compromises both abducting and adducting functions as a consequence of laryngeal muscle denervation. In most of these patients, random regeneration of neural fibers in the RLN results in aberrant reinnervation of laryngeal muscles. In such a synkinetic larynx, contraction of abductor and adductor antagonists produces ineffective, unsynchronized or even opposite movement of the vocal fold(s) [7]. Since the number of adductor muscle fibers are approximately 4 times greater than the number of abductor muscle fibers, it is anticipated that the adductors will receive greater reinnervation by any motoneuron type, including both glottal closure and opener motoneurons. This is the reason the vocal folds tend to assume a paramedian position statically. When the involvement of vocal folds is bilateral, patients end up with severe airway compromise and require timely intervention.

The primary objective of intervention for BVFP is to improve patients' ventilation. Various surgical procedures have been developed to address the airway restriction seen with BVFP. Tra-

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cheostomy remains the most commonly used procedure in the early onset period when nerve recovery is still hopeful. Although tracheostomy has its obvious downsides for patients, it provides the largest airway and maintains the structural integrity of the glottic larynx. Since the beginning of the 20th century, other approaches to enlarge the stenotic airway have been introduced, first with external methods and later with endoscopic techniques. In addition, new techniques such as laryngeal pacing and reinnervation procedures have also been studied and applied in some cases of BVFP [8,9]. In recent years, botulinum toxin (Botox) injection has been used in patients with laryngeal synkinesis. Other treatment approaches currently being investigated include gene therapy and stem cell therapy. These various treatment options are reviewed below.

TRACHEOSTOMY

Tracheostomy is one of the most common surgical interventions for BVFP. Despite its effectiveness, tracheostomy is now becoming less favored by most patients because it presents an open wound that requires long-term care and creates psychosocial problems [9]. Patients experience decreased quality of life and must engage in continual postoperative management of their tracheostomies [10,11]. Recent evidence has shown tracheostomy is less cost-effective compared to endoscopic techniques (i.e., cordotomy and arytenoidectomy) in management of BVFP [12]. Nevertheless, tracheostomy is still indicated as an effective, emergent, and initial method for management of BVFP over the short term [13].

ARTENOIDECTOMY

The arytenoid cartilage is a key structure of the posterior glottis. Removal of arytenoid cartilage (i.e., arytenoidectomy) is a permanent and irreversible surgical procedure, by which the glottal inlet is expanded in its transverse axis, providing a larger airway for respiration [8]. Arytenoidectomy is widely used either alone or in combination with partial resection of the vocal fold (i.e., arytenoid cordectomy).

Resection of the arytenoid cartilage had been performed through an open-neck approach since early 1900s [8,14-18]. In

1948, Thornell [19] described the first endolaryngeal arytenoidectomy through the endoscopic approach. His technique later became the most widely accepted strategy for endoscopic arytenoidectomy. A temporary tracheostomy was used in the early perioperative period with his approach. The glottis is widened by partial mucosal resection over the arytenoid area extending into the aryepiglottic fold. This technique, along with its various modifications [14,20], demonstrated good results in terms of ventilatory improvement in patients with BVFP [21]. Arytenoidectomy was further advanced by application of lasers in surgery. The major advantage of using the CO₂ laser include the precision of laser incision, the capacity to maintain hemostasis, and decreased postoperative edema [22,23]. In 1983, Ossoff et al. [24] first described the total arytenoidectomy procedure using the CO₂ laser endoscopically. In Ossoff's technique, after ablation of the majority of the arytenoid, the incision was extended laterally to induce fibrosis, which retracted the vocal fold laterally [8,24]. Modifications to Ossoff's technique have been reported by other clinicians [25,26]. In particular, Crumley [27] proposed endoscopic laser medial arytenoidectomy with minimal resection of the vocal fold. In this technique, a resection of the medial part of the arytenoid body was performed by preserving other aspects of the cartilage, including vocal process. This aimed to provide maximal preservation of the phonatory structures. Nonetheless, deterioration in voice quality was documented in a great proportion of patients [22,28,29]. In addition, arytenoidectomy was susceptible to granuloma and scar formation, which led to re-narrowing of the airway. In this case, one or more revision surgeries were usually required [8]. In comparison with other extralaryngeal techniques to perform arytenoidectomy, endoscopic laser resections did not differ significantly in terms of functional outcomes, but had a significant advantage that tracheostomy was not required [8]. Avoidance of tracheostomy or successful decannulation could be achieved in the majority of patients [29,30]. Use of an endoscopic plasma coblator instead of laser induced less scar formation by avoiding thermal damage to surrounding tissues [31], but a large-scale patient study with this technique has not been performed.

CORDOTOMY

Like arytenoidectomy, cordotomy (i.e., posterior cordotomy and transverse cordotomy) is another irreversible surgical approach that aims at enlargement of the airway aperture at the glottic level by excision of tissues. Cordotomy is different from arytenoidectomy in that the former approach aims at resection of laryngeal soft tissues, such as parts of the vocal fold, the vocal ligament, or the thyroarytenoid (TA) muscle [8]; while the latter approach mainly focuses on arytenoid cartilage ablation. Sometimes they are performed conjointly (i.e., arytenoidcordectomy).

Resection of a large portion of the vocal fold was performed

HIGHLIGHTS

- Patients with bilateral vocal fold paralysis are dyspneic and require timely intervention.
- The primary goal is to improve patients' ventilation. Surgery is the mainstream of treatment.
- Current treatment options are reviewed in this article.

as a treatment approach for BVFP as long as a century ago. Soon thereafter, dissection focused on the sub-mucosa to preserve the overlying mucosa and minimize subsequent scar formation and voice disturbance [8]. After the introduction of a transoral approach for laser arytenoidectomy [24], Dennis and Kashima [32] followed suit with their introduction of a modern endoscopic laser cordotomy technique in 1989. They performed the CO₂ laser posterior cordotomy by resecting the soft tissues of the posterior vocal fold and transecting the conus elasticus. In this technique, a C-shaped wedge of posterior vocal fold was excised from the free border with a lateral extension of a couple millimeters to release soft tissue tension on the vocal fold [8]. Improved ventilation was achieved in most patients with BVFP following cordotomy [32-35]. Over 60% of patients were decannulated [32, 34,35]. Like arytenoidectomy, however, cordotomy was susceptible to granulation and scar formation. It was reported that bilateral or revision cordotomies were needed in about 30% of patients due to decreased glottal opening from formation of scar tissue or granulation [9,32,33]. Another most commonly seen side effect associated with cordotomy was deterioration of voice quality [34-36]. Patients often complained of a rough and breathy voice because of damage to the vibratory part of the operated vocal fold [37].

Laser endoscopic cordotomy has become the preferred therapeutic intervention for long-term management of BVFP. In comparison to arytenoidectomy, cordotomy is preferred because it is less destructive and there is less tendency for aspiration. Cordotomy can be proposed as an alternative to tracheostomy even at the time of diagnosis. However, it should be emphasized that the level of ventilation permitted through a cordotomy is usually less than that through a tracheostomy. Further, vocal fold resection impairs voice quality and puts the patient at some risk for aspiration. In addition, revision interventions are often required due to granulation or formation of scar tissue, which retract the vocal fold to the median position [8,9]. Although cordotomy has been modified by otolaryngologists to improve patients' ventilation and maximize the preservation of their voice quality, this treatment approach is less than ideal [36,37].

LATEROFIXATION OF THE VOCAL FOLD AND/OR THE ARYTENOID CARTILAGE

Laterofixation (i.e., suture laterofixation and suture lateralization) of the arytenoid and/or the attached vocal fold using a combination of endoscopic and external means has emerged as an alternative surgical approach for BVFP [38]. In recent years, it has been performed in adult and pediatric patients with good success rates [39,40]. Due to its reversible nature, laterofixation is favored by many BVFP patients as a temporary management of the airway, based on the fact that spontaneous recovery could be expected in 40%–86% of cases if the RLNs have not been transected [8,41].

According to a review by Sapundzhiev et al. [8], Rethi reported the lateralization of arytenoid through a laryngofissure dissection in 1922. Ejnell and his associates [42,43] performed suture lateralization using a small endotracheal tube without the need for a tracheostomy. In this technique, the larynx was exposed by direct laryngoscopy and the cricoarytenoid joint assessed by palpation. After removal of the TA muscle, sutures were introduced into the larynx through 2 needles inserted from outside. The sutures were pulled out through the laryngoscope and knotted to lateralize the vocal fold [44]. In 1983, Lichtenberger [40,45] introduced a needle carrier capable of passing a needle and suture endolaryngeally through the thyroid ala to the skin, thereby significantly simplifying the procedure. Specifically, following endoscopic exposure of the larynx, a longitudinal incision was made on the superior surface of the vocal fold and the TA muscle was removed. Using a curved tip needle carrier, one end of the suture was pushed through the larynx below the posterior third of the vocal fold and the other end was pushed through above the vocal fold. Both ends of the fixation suture were pulled and knotted over the strap muscles. A second lateral fixation suture was placed 1–2 mm anterior to the first suture using the same technique. Over past years there have been several procedural modifications to this technique [36,46-52]. In particular, Woodson and Weiss [53] and Woodson [54] proposed their technique called “arytenoid abduction.” This technique is based upon the fact that residual muscle motion is often partially preserved in adductor muscles following RLN injury, as adductor motor fibers are 4 times more plentiful than the abductor fibers in the RLN [2]. Their technique is to perform suture laterofixation of the arytenoid cartilage, which provides posterior-caudal traction (simulating the contraction of the posterior cricoarytenoid [PCA] muscle) to abduct the vocal fold. Meanwhile, closure of the glottis during phonation and swallowing can be achieved by voluntary control of the adductor muscles [54]. This technique, although relies primarily on the recovery of adductor function, is still a promising intervention that can restore dynamic motion of the paralyzed larynx [53].

Laterofixation can be performed independently or coupled with other endoscopic procedures, such as arytenoidectomy [46,47,55]. Compared to static procedures (i.e., cordotomy and arytenoidectomy), enlargement of glottal opening and improvement of aerodynamic measures are significantly greater in patients following laterofixation. In addition, laterofixation provides better phonatory closure of the vocal folds that perhaps leads to better voice quality [36,39,54]. Risk of aspiration appears to be low [48,54,56]. The rate of re-operation was reported to range from 10%–30% [40,50,52].

Suture laterofixation is potentially reversible so that it may serve as an alternative to tracheostomy. Lateralization of vocal fold and/or arytenoid cartilage enlarges the airway without damaging phonatory tissues, thus preserving the option of voice restoration by reversal of the procedure. It can be applied bilat-

erally or with other endoscopic procedures as needed [57]. The incidence of adverse events (e.g., hoarseness, aspiration, dysphagia, and revision surgery) are relatively low compared with other static procedures. Arytenoid abduction may even preserve the dynamic motion of the larynx. In all, suture laterofixation is indicated for patients with BVFP when recovery of laryngeal function is expected or avoidance of tracheostomy is preferred [39].

REINNERVATION

No glottic enlargement techniques based on resection restore both major functions of the larynx, specifically, enlarging the airway for inspiration and closing it for vocalization and swallowing. In this regard, procedures for reinnervating laryngeal muscle have been investigated to restore the voluntary motion of the larynx. In fact, the primary goal should be to re-establish the vocal fold abduction through reinnervation of the abductor (PCA) muscle, as dyspnea is the major symptom in most of these patients whose adducting function is partially preserved. Laryngeal reinnervation, although developed primarily for treatment of UVFP, may also be applied in BVFP patients.

Anastomosis of the RLN was reported about a century ago [58], but there have been limited studies in this area, possibly due to the variability and complexity of nerve supply [59]. Results of human trials are sparse and only based on case series. Miehlike [60] developed a technique for RLN anastomosis in animal studies and subsequently applied it to the human. In this technique, the distal posterior RLN branch innervating the PCA muscle was transected and anastomosed with the main funiculus of the RLN dissected out of the vagus trunk and transected. The distal anterior RLN branch innervating the adductor muscles was then transected [59]. However, this technique has not been further explored by other researchers, possibly due to its complexity in practice.

Attempts have also been made using foreign nerves to reinnervate the PCA muscle. Phrenic nerve is a good source of nerve supply as it contains a homogeneous composition of motoneurons that are active during inspiration [59]. A recent study from China was conducted in 44 patients with BVFP to assess the efficacy of PCA muscle reinnervation using the left phrenic nerve [61]. Results seemed promising in that inspiratory vocal fold abduction was achieved in 41 cases (93%). Although the patients suffered from hemi-diaphragm paralysis, they had substantial recovery of diaphragm motion (40%–82%) and respiratory function within 1 year. Marina et al. [59] further demonstrated that phrenic nerve roots innervating the diaphragm were mainly distributed in C3-C5. Therefore, only a branch of the phrenic nerve may be taken to minimize loss of diaphragm motion and respiratory capacity.

Perhaps the most explored and applied reinnervation procedure is transplanting an active nerve-muscle pedicle to the PCA

muscle harvested from an accessory muscle of inspiration (i.e., omohyoid or sternohyoid) [8]. Increased glottic airway was observed in over 80% of patients, presumably because the transferred nerve-muscle pedicle was activated during hypoxic conditions [62,63].

In summary, laryngeal reinnervation appeared to be a promising surgical approach for BVFP patients. However, the evidence of success in humans is limited, thus more clinical trials are needed before any other conclusion may be drawn.

LARYNGEAL PACING AND FUNCTIONAL ELECTRICAL STIMULATION

Functional electrical stimulation (FES) of paralyzed laryngeal muscles has been investigated over the last 4 decades [64-66]. In 1977, Zelear and Dedo [64] first introduced the concept of FES of paralyzed head, neck and thorax muscles. Their model was the unilaterally paralyzed cricothyroid muscle of the canine. Subsequently, this idea was translated to stimulation of the paralyzed PCA muscles in the canine model of BVFP, termed laryngeal pacing [65,67,68]. It was then shown in BVFP canines chronically implanted with stimulators, that bilateral PCA activation could restore ventilation and exercise tolerance to normal without any aspiration over the long term [69,70]. Zelear et al. [66] first confirmed laryngeal pacing was an effective means of treatment in the human using an external device. Shortly thereafter, his team conducted the first human trial of unilateral laryngeal pacing in 7 patients with BVFP implanted with a commercial stimulator and electrodes [71]. Results demonstrated that unilateral pacing was an effective treatment superior to posterior cordotomy with respect to postoperative ventilation and voice outcome measures [37]. Mueller and his associates [72,73] recently conducted a clinical trial of unilateral pacing in 9 patients with BVFP. They used minimally invasive electrodes activated by an external pacemaker affixed to the chest wall. Significant improvement in ventilation with no negative effect on voice quality was noted.

In summary, these animal trials and pioneer clinical cases demonstrated clearly the feasibility of FES in the treatment BVFP. Future studies may involve a multicenter clinical trial of laryngeal pacing.

BOTULINUM TOXIN

Botox is a neurotoxin produced by the *Clostridium botulinum*. There are 7 serologically distinct toxin types (A-G). Type A and B are the forms most frequently used clinically. The toxin prevents the release of acetylcholine from axon terminals and thus causes flaccid paralysis [74]. It was first introduced for medical use in the 1980s [75]. In case of BVFP, Botox may be used to

block aberrant reinnervation of the adductor muscles by inspiratory motoneurons. In this way, the abductor inspiratory motoneurons would gain advantage and become more effective in producing glottal opening [74,76].

Marie et al. [77] first described a case of Botox injection into bilateral adductor muscles as a treatment for BVFP. Improvement in ventilation was seen in this patient. Zeale et al. [76] also used Botox in their study of human laryngeal pacing to counteract the stimulated adduction of the vocal fold due to spread of stimulus current. They also noted an increase in the unstimulated passive airway with an improvement in ventilation due to blockade of the adductor muscles. A subsequent study of adductor muscle Botox injection in 11 BVFP patients demonstrated symptomatic improvement in ventilation with breathy dysphonia [78]. The reported dosage was at least 2.5 mouse units for each vocal fold. Overall, Botox injection appeared to provide an acceptable, but temporary (around 3 months) improvement in glottal opening [76]. Therefore, with repeated injections, patients may enjoy ventilatory improvement over a longer period of time. Additional studies are needed to compare the outcome of Botox injection with that achieved by other surgical interventions [74].

NEUROMODULATORY EFFECT OF ELECTRICAL STIMULATION IN PROMOTING SELECTIVE REINNERVATION OF THE DENERVATED PCA MUSCLE IN BVFP

Electrical stimulation has emerged as a potential therapeutic measure following peripheral nerve injury. It has long been established that electrical stimulation improves functional recovery of denervated muscles by accelerating axon regeneration and reinnervation of muscle before significant atrophy occurs [79-85]. More recent evidence has revealed that electrical stimulation may also promote the specificity of reinnervation of denervated laryngeal muscles. This is an important finding since 70% of BVFP patients become synkinetically paralyzed despite successful reinnervation. Zeale et al. [86] first showed that synkinesis could be avoided by stimulating the muscle or its reconnecting motoneurons in the canine. In a second study [86,87], quantitative evidence was obtained demonstrating that low frequency stimulation of the PCA muscle repressed reconnection by foreign reflex glottic closure (RGC) motoneurons and promoted reinnervation by native inspiratory motoneurons. In a subsequent study using a canine model of BVFP, low frequency stimulation (i.e., 10 Hz) of denervated PCA muscles was shown to improve functional recovery. Specifically, the selective reinnervation of muscles minimized paradoxical closure of the glottis during inspiration and restored exercise tolerance to normal [88]. EMG recordings showed a near normal pattern of low PCA and high TA reinnervation by RGC motoneurons in 10 Hz

animals. In contrast, nonstimulated controls and 40 Hz stimulated animals had faulty reinnervation, severe paradoxical closure of the glottis during hypercapnia, and poor tolerance to exercise. Such findings may offer a physiologic and natural approach to treatment of BVFP. It should encourage further investigation of FES neuromodulation to improve voluntary function and avoid synkinesis by stimulating the PCA muscle during a critical period of regeneration following RLN injury.

GENE THERAPY

Gene therapy for BVFP presents the idea of delivering genes to the injured neurons and/or denervated muscles, thus enhancing the regrowth of these damaged neurons and rejuvenating laryngeal muscles. These genes typically encode neurotrophic factors that promote neuronal survival, or growth factors stimulating muscle cell proliferation and differentiation [89]. The therapeutic genes are delivered by vectors injected into the RLN or laryngeal muscles. There they are absorbed by the muscle cells, or by the neuronal cell bodies via retrograde axonal transport [90-92]. After these genes are transduced into the nucleus of the target cells, they produce peptides that promote RLN regeneration, synaptic formation, and muscle growth.

Preliminary attempts have been made to investigate the effect of gene therapy for RLN injury in animal models. Shiotani and his associates [93-95] have investigated insulin-like growth factor I gene transfer in rats' denervated larynges. They injected the gene using a polyvinyl-based delivery system into the denervated TA muscle. Compared to the controls, treated animals demonstrated a significant increase in the diameter of muscle fibers and the percentage of end plates contacting axons in the TA muscle [93-95]. In a subsequent study in rat, they injected an adenoviral vector encoding glial cell line-derived neurotrophic factor (GDNF) into nucleus ambiguus following vagus nerve transection. The treated animal demonstrated a significant reduction in the loss of nucleus ambiguus motoneurons at 4 weeks after injection. The GDNF-gene treated animals also showed higher inhibition of nitric oxide synthase activity and better preservation of choline acetyltransferase immunoreactivity, both indicating greater recovery of nerve function [96]. Further, they injected adenoviral-tagged GDNF into the crushed RLN in a rat model. The treated animals had significantly improved nerve conduction velocity and higher percentage of vocal fold motion recovery up to 4 weeks. The treated rats also showed a significantly larger axonal diameter and improved remyelination over controls [97].

Currently, the major bottleneck of gene therapy in the treatment of BVFP is its null effect in preventing synkinesis [90]. In addition, study may also be needed to minimize neuronal damage by delivery of viral vectors into the CNS. As of now, this technique may potentially benefit patients with BVFP caused by neurodegenerative diseases.

STEM CELL THERAPY

Stem cell transplantation has been recognized as a therapy by allowing tissue regeneration. Stem cell therapy may offer improved healing potential in degenerative tissue. For instance, autologous stem cells can be isolated from small samples of tissue from patients, cultured to a critical mass and re-implanted. Muscle stem cells may promote regrowth of atrophic muscle mass and provide a better platform for reinnervation.

Halum et al. [98] introduced use of autologous muscle-derived stem cells (MSCs) for the treatment of VFPP in 2007. They successfully isolated, cultured and labelled MSCs before injecting them into denervated TA muscles in rats. These cells survived and

were incorporated into the muscle alongside atrophying fibers at 2 months. This incorporation attenuated the overall muscle atrophy in comparison to non-treated controls. Two of 8 treated rats showed a weak vocal fold adduction upon activation of the glottal closure reflex, while none of the control animals exhibited such a response. Dirja et al. [99] explored the use of induced pluripotent stem (iPS) cells as an alternative to MSCs. The labeled iPS cells successfully differentiated into skeletal muscle cells *in vitro*. These cells were then transplanted into the atrophied TA muscle and survived for 2 weeks in rats. Gotoh's team injected adipose-derived regenerative cells into the denervated vocal fold of the pig. Remarkable hypertrophy of the TA muscle fiber was observed around the injection site at 1 month [100].

Table 1. Summary of treatment options for BVFP

Treatment modality for BVFP	Indication	Pros	Cons
Tracheostomy	Acute dyspnea; temporary management of BVFP	Immediate relief of airway obstruction; greater improvement of ventilation compared to static procedures; no revision surgery required	Destructive of normal tissues; psychosocial impairment; scar formation; daily care of open wound required; decreased quality of life
Arytenoidectomy	Permanent management of BVFP; patients who want to be decannulated or avoid tracheostomy	Quick, effective enlargement of glottis to return breathing through mouth without dyscosmesis; can be combined with cordotomy; more cost-effective than tracheostomy	Irreversible; deterioration of voice; scar or granuloma formation; aspiration; may need revision surgery
Cordotomy	Permanent management of BVFP; patients who want to be decannulated or avoid tracheostomy	Quick, effective enlargement of glottis to return breathing through mouth without dyscosmesis; can be combined with arytenoidectomy; more cost-effective than tracheostomy; less tendency for aspiration than arytenoidectomy	Irreversible; deterioration of voice; scar or granuloma formation; aspiration; may need revision surgery
Laterofixation	Temporary management of the airway, with expectation of recovery of laryngeal function or avoidance of tracheostomy	Reversible; alternative to tracheostomy; greater improvement of airway, better voice quality, and less revision rate than arytenoidectomy and cordotomy; may be performed with other endoscopic procedures	Complications such as hoarseness, need for adjustment, remedialization, dysphagia or aspiration
Reinnervation	Patients that have non-atrophic viable muscles maintained through synkinetic reinnervation	A promising procedure that may allow return of spontaneous vocal fold abduction; non-destructive and doesn't impair adductory functions	Technically more difficult; human trials are limited; potential diaphragmatic paralysis
Laryngeal pacing	Patients that have non-atrophic viable muscles maintained through synkinetic reinnervation	Greater ventilatory improvement reported than any other approach; no compromise of voice or swallowing	Still experimental with only 2 human trials; complicated procedure; more expensive than enlargement or lateralization approaches; device has to be replaced every 5–10 years
Botox injection	Temporary management of synkinetic larynx	Less invasive; short-term improvement in ventilation; little effect on voice or swallowing	Repeated injections are required; human trials are limited
Neuromodulation	Recently injured RLNs; muscles still denervated and nerve regenerating prior to synkinetic reinnervation	From canine studies, electrical neuromuscular conditioning promotes selective reinnervation of muscles, minimizes synkinesis and restores ventilation to normal	Experimental; no human trial
Gene therapy	BVFP caused by neurodegenerative diseases	Less invasive; could promote nerve regeneration and prevent muscle atrophy	Experimental; no human trial; not effective in preventing synkinesis; neuronal damage by viral vectors
Stem cell therapy	BVFP caused by neurodegenerative diseases	Could promote nerve regeneration and prevent muscle atrophy	Experimental; no human trial; not effective in preventing synkinesis; issues associated with isolation, culture and survival of stem cells

BVFP, bilateral vocal fold paralysis; Botox, botulinum toxin; RLN, recurrent laryngeal nerve.

Similar to gene therapy, the application of stem cell therapy for BVFP is largely limited by its null effect in preventing synkinesis. So far little is known about its effect on the reinnervation pattern of laryngeal muscles. Further investigation is required before it can be considered as a treatment option for BVFP.

SUMMARY

The treatment options for BVFP are summarized in Table 1. Static glottis enlarging procedures, which function by either resection of laryngeal tissues (i.e., arytenoidectomy and cordotomy) or displacing anatomical structures (i.e., suture laterofixation of vocal fold or arytenoid abduction), are most commonly used as they provide an immediate effect of airway improvement regardless of the innervation status of laryngeal muscles. The common side effects associated with such procedures are dysphonia, dysphagia, and aspiration. Suture laterofixation of vocal fold is more favorable than the other static procedures in that it is reversible and minimally impairs adductor functions: voice and swallowing. Further, it may be considered as an alternative for tracheostomy for patients with good prognosis for spontaneous reinnervation. Other new techniques, such as reinnervation, laryngeal pacing and Botox injection, are still experimental. They are indicated in BVFP patients who have laryngeal muscle reinnervation that is synkinetic. Nevertheless, they provide promising therapies for the treatment of BVFP. Specifically, these techniques represent a more physiological approach to recovery of laryngeal function without necessitating tissue damage. Selective reinnervation of the PCA muscles by inspiratory motoneurons within a branch of the phrenic nerve represents a more natural approach to reverse synkinesis in BVFP. Further, neuromodulation of the reinnervation process by electrical stimulation has been shown to promote selective reinnervation by original motoneurons and avoid synkinesis altogether. Although the goal is to cure paralysis, no clinical trial has been conducted with this novel technique as yet. The emergence of gene therapy and stem cell therapy reflects new ideas in treatment for BVFP by promoting regrowth of neurons and atrophic muscles. However, both techniques are limited by their null effect in preventing synkinesis. Further study in both animals and humans will be needed to explore their potential benefits for BVFP. In the future, patients with BVFP are expected to benefit from the advancement of those new treatment approaches, and have a better quality of life.

CONFLICT OF INTEREST

Dr. Zealear has a conflict to disclose. An Food and Drug Administration (FDA) approved clinical trial of laryngeal pacing is in progress through a contract with St. Jude Medical Inc. As patent inventor and principal investigator on the project, Dr. Zealear

will receive royalties on sales if the commercial phase is reached with this technology. Neither of the other authors have a conflict of interest.

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