Active and Passive Bioimplants for Vocal Fold Paralysis

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ABSTRACT

Vocal fold paralysis is one of the diseases that particularly affect the quality of life. While unilateral paralysis leads to glottis closure insufficiency and hoarseness, bilateral paralysis compromises respiration and limits the exercise tolerance. Bioimplants have been used to treat persistent paralysis for over 100 years. The spectrum ranges from autologous tissue transfer and resorbable or permanent injection materials to composite thyroplasty implants and active electrical implants for neurostimulation of the larynx. If bioimplants are used in accordance with the recommendations, the quality of life of the affected patients can be significantly improved today.

Contents

1. Unilateral recurrent laryngeal nerve paralysis

Unilateral vocal fold paralysis leads to insufficient glottis closure with air loss in the context of speaking, reduction of the voice range, pitch and volume, reduction of the maximum phonation time and audible breathiness of the voice. The result is a weak voice that tires quickly and the risk of pathological compensation of the insufficient glottis closure by using the false vocal folds. The severity of the complaints mainly depends on the position and tension of the vocal folds. Initially, the voice may be aphonic and proneness to aspiration may be observed.

In daily routine, less attention is paid to the fact that at the same time a unilateral abduction inhibition exists that limits the max. diameter of the glottic opening. In cases of unfavorable, widely median position and high tension, some patients complain about breathing difficulties in the context of high physical exercise.

In most cases, compensation or ideally even complete restoration of the motility may be achieved. The focus of this article is placed on those cases where conservative speech therapy does not lead to sufficient improvement and bioimplants are applied for vocal fold medialization.

1.1 Injection laryngoplasty

The term of injection laryngoplasty defines the injection of biomaterials or autologous tissue transfer into paralyzed vocal folds for augmentation of the vocal fold volume with the objective to restore a complete glottis closure for phonation. According to Choi et al. [1], the benefit from augmentation is significantly increased in younger patients (< 65 years) and those with mild glottis gap. This authors defined the glottis gap as mild when the distance between the vocal processes was smaller than half of the width of the healthy vocal fold.

The German ENT surgeon Brünings is considered as the founder of injection laryngoplasty. Already in 1911, he described the augmentation of the vocal fold with paraffin oil [2]. In 1985 for the first time, Teflon injection into the vocal folds was performed in awake patients under local anesthesia in the USA [3]. The technique of Teflon injection was applied very frequently in the 20ies century because it was technically well applicable and had a lasting augmentation effect, however, due to the relevant number of giant cell granulomas, this approach was abandoned [4]. Teflon granulomas as foreign body reaction may develop even decades after injection. The inflammation only stops when the Teflon and the surrounding granulation tissue are completely removed. The long-term sequelae for the voice seem to be obvious.

The ideal substance for vocal fold augmentation has not yet been found. Not all routinely applied substances for vocal fold augmentation have been developed for application in the larynx. Due to the missing conformity confirmation of the European Community (CE, Communauté Européenne), their usage is considered as therapeutic application of biomaterials outside the indication spectrum (off-label use), even in cases of existing FDA approval (Food and Drug Administration). According to the author's experience, the frequently used classification into temporary and permanent injection materials is not finally clarified. The data situation in the literature regarding resorption rate, effect duration, and biological interaction of the autologous, xenogenic, and alloplastic substances that are currently applied for injection laryngoplasty are still insufficient. In a meta-analysis published by Wan-Chiew et al. in 2021 [5], the authors assessed 6,240 publications on biomaterials that have been developed for vocal fold augmentation since 2010. The authors concluded that statements on the viscoelasticity are made without referencing them to the clinical effect. Studies about the biological absorption (effect duration), cell interaction, and inflammatory reactions (side effects), however, are insufficient and should be initiated in time when future augmentation materials are developed.

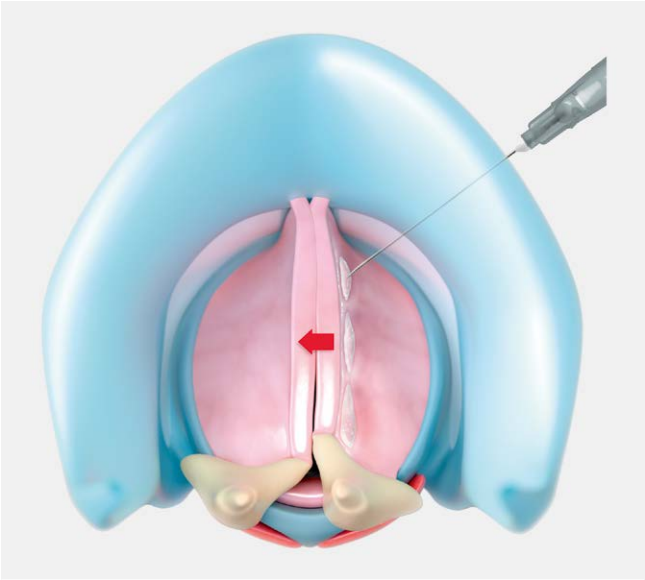
1.1.1 Temporary vocal fold augmentation

Within 4–6 months, up to 75 % of the patients with unilateral paralysis regain phonation that is sufficient for their vocal needs although the percentage of the vocal fold motility restoration is significantly lower (33–40 %). However, in clinical routine there are a number of patients who do not achieve a satisfactory glottal closure with speech therapy allone but develop a compensatory hyperfunction with excess use of supraglottic sphincters. Besides, there is a growing number of patients who professionally use their voice and who have high demands to the restoration of the voice function. In these cases, the option of temporary vocal fold augmentation should be discussed early. In accordance to Hess et al. [6], we started to offer this therapy option already at the time of diagnosis. In this way, the subsequent speech therapy is facilitated, the patients can work earlier in their voice-depending job and perceive the improvement of their voice quality directly after the diagnosis of a paralysis.

During the last century, numerous materials have been tested and applied for temporary vocal fold augmentation. Materials with short-term effect are fibrin glue that is nowadays used rather for vocal fold scars and phonosurgery and bovine gelatin that is preferred in the USA (Gelfoam, Surgifoam) and that has mostly been replaced by carboxymethyl cellulose (Radiesse Voice Gel) [7]. None of these materials is CE approved.

Collagen and hyaluronic acid materials are considered as having an intermediate effect (see ▶ **Fig. 1**). Their effect duration is often given with 3–4 months. Even longer augmentation effects have been observed in clinical practice.

The application of bovine collagens (Zyplast, Cymetra and others) requires compatibility testing three weeks before use. The reason for this previous skin test is the risk of type IV allergic reactions because about 3 % of the population are already sensitized against bovine collagen before collagen treatment. The augmentation with this biomaterial should not be performed by injection into the muscles but into the lamina propria because resorption occurs more quickly in the muscles. In cases of superficial injection into the vocal fold, inflammation in Reinke's space may develop with restriction of the mucosal wave and subsequent organic dysphonia [8]. In medicine, porcine collagens are applied rather as matrix materials for example for camouflage of the nasal dorsum in rhinoplasty (Permacol). However, they cannot be used in all patients, also due to religious reasons. Alternative options are human recombinant collagens that are gained transgenically via plants or bacteria (CosmoPlast/CosmoDerm) [9]. Due to their instability, they are mostly combined with hyaluronic acid in plastic surgery [10].



▶ **Fig. 1** Temporary augmentation of the vocal fold with hyaluronic acid or similar temporary fillers.

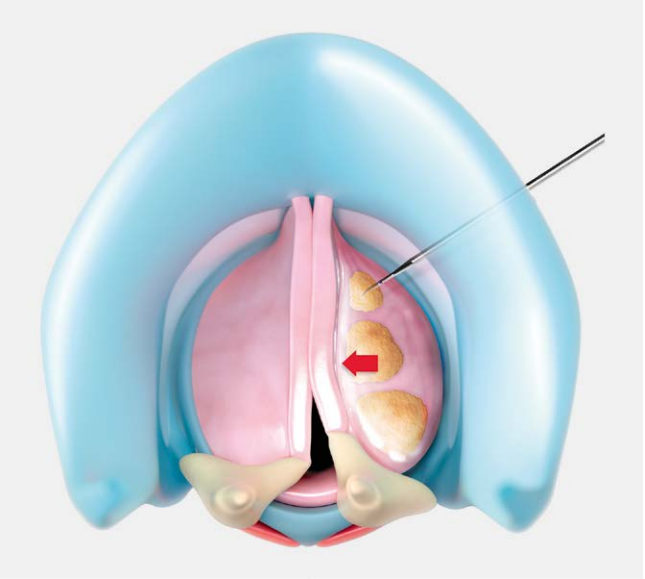
Due to the disadvantages of collagens, predominantly hyaluronic acid preparations are currently used (Restylance, Hyalaform, Juvederm, and others) for temporary vocal fold augmentation [11–15]. Depending on the chosen brand, hyaluronic acid is mostly well tolerated, has a suitable viscosity, and allergy tests prior to application are not necessary. Preparations from this substance group are frequently used in esthetic surgery as fillers for wrinkle treatment. Therefore, a lot of experience regarding tissue tolerance is available. According to the author's knowledge, these preparations are CE certified but none of them has been approved for the indication spectrum of vocal fold augmentation. This means that the application of this important group of substances is currently also off-label. Patients must be informed comprehensively about this circumstance. If augmentation of the vocal folds with these off-label substances is the only reason for treatment, there might be problems with reimbursement by the health insurances.

Calcium hydroxyl apatite microspheres (Renu Voice) is another substance coming from the field of esthetic wrinkle treatment. It was specifically approved for vocal fold augmentation based on CE criteria and may thus be applied in-label. In a recent article by Miaskiewicz et al. [16], the authors compare the long-term effect of hyaluronic acid (HA) with calcium hydroxyl apatite (CaHA). They found a surprisingly long-lasting effect of both substances over the follow-up period of 24 months. Only in 12.5 % of the CaHA and in 9.3 % of the HA augmentations, re-augmentations were necessary. These results may be interpreted in two different ways. On one hand, the resorption time of HA and CaHA might have been estimated wrongly in the vocal fold tissue. The present studies on the resorption of HA refer to esthetic application in the face and of CaHA to animal experiments [17, 18]. On the other hand, re-innervation starting in parallel to the partial or complete resorption of the augmentation materials may contribute to better toning and volume increase of the vocal fold, even if it does not lead to restoration of the motility, and thus mimic a residual augmentation effect. Histological examinations in this field are not available.

An intermediate position between temporary and permanent augmentation may be assumed by substances that may cause volume preservation or increase of the vocal fold by interaction with the tissue. This group of substances includes growth factors like the basic fibroblast growth factor (bFGF) that, according to animal experiments, increases the number of end plates in the re-innervation phase of recurrent laryngeal nerve paralyses and is said to have a regenerative effect on nerve and muscle fibers. In the placebo-controlled trial performed by Hirano et al. [19], a significant cross-section increase of the thyro-arytenoid muscle could be observed within 4 weeks. An increase of the autogenous hyaluronic acid production in the lamina propria could be confirmed by Kanazawa [20] for scars, sulcus, and paralyses. However, the author of this contribution does not know about any application of xenogeneic or recombinant human fibroblast growth factors in humans in Europe for this purpose [21]. Growth factor inhibitors are approved for the field of oncology. Beside the growth factors, pluripotent stem cells and especially mesenchymal stem cells from fatty tissue (ASC) might play a role for the regeneration of vocal fold paralyses [22] in the future. In order to avoid excessive scar formation after phonosurgical interventions for reconstruction of the vocal folds, such lipid fraction containing stem cells are already applied [23].

1.1.2 Permanent vocal fold augmentation

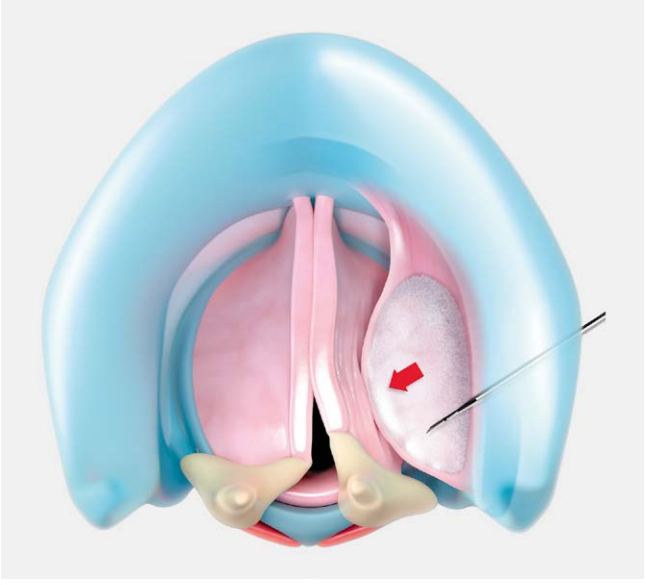
Despite the limiting factor that important resorption has to be considered also for these materials, augmentation of the vocal fold by means of autologous fat or fascia is classified as permanent procedure. Generally, permanent augmentation should only be applied when spontaneous recovery of the recurrent laryngeal nerve paralyses can no longer be expected or persistent damage of the nerve due to previous diseases or surgeries is known.



▶ **Fig. 2** Fat augmentation into the thyroarytenoid muscle (TA) in several deposits (yellow); overcorrection due to fat resorption must be considered.

Autologous fat is biocompatible, cheap to gain, and non-toxic [24]. The disadvantage is the initial resorption rate that cannot be predicted. Therefore, in general over-correction is planned. For extraction of fat material, there is the early applied procedure of manual taking of small fat portions by means of scalpel and washing out of lipid cells. In plastic surgery, the objective was to separate cellular debris and liquid from intact fat cells that should be transplanted preferably. Due to the diameter of the injection cannulas (18–20 G) and the mechanical stress of the transplanted material in the vibrating vocal fold, this procedure must be considered as rather hypothetic. In the last years, the manual preparation was abandoned and replaced by periumbilical liposuction. Hereby, the extracted fat is centrifuged with 3,000 rpm for 3 minutes [25]. This method is applied in plastic surgery and is suitable for production of well injectable biomaterial for application at the vocal fold. By separating the material into three fractions, the heavy cellular debris remains on the bottom of the syringe, in the middle the fat and stem cells are found, and on the top the lighter fat. Only the middle part is used for augmentation. For this method, a specific set for extraction and injection is provided (VoiceInject) [26]. Compared to all permanent augmentations, the injections are generally performed in the context of microlaryngoscopy under general anesthesia (see ▶ **Fig. 2**). However, in cases of risks for general anesthesia it is also possible to perform fat extraction under tumescence anesthesia and the injection by flexible endoscopy under sedation [26]. Due to the long way through the injection catheter needle inserted in the working canal (23 G), more fat is required, and a high-pressure pistol must be used for insertion of the material. According to our experience, the effect duration varies enormously. After 12–24 months, re-augmentation must be expected.

A similar approach is pursued with the application of pieces of autologous temporalis fascia or fascia lata [27]. The manual preparation until injection is more extensive compared to fat but especially regarding long-term stability the results are better. Gneid et al. [28] describe an effect duration of 3–10 years in more than 500 interventions which is significantly longer than with fat and has the same tolerance. Nonetheless, this method could not prevail, probably because of the extensive preparation and the risk of blocked cannulas. Currently, the application of fascia, fat, perichondrium, cartilage in combination or together with growth factors is further investigated in animal experiments or clinically in cases of scars or wounds of the vocal folds. It remains to be seen which autologous material will have the most important clinical significance in the future.



▶ **Fig. 3** Permanent augmentation with silicone microspheres (VoxImplant – whitish) widely lateral between the thyroid cartilage, lateral thyroarytenoid muscle (LCA), and thyroarytenoid muscle (TA).

Regarding alloplastic biomaterials for permanent vocal fold augmentation, the use of polymethyl dioxane (silicone) micro particles in suspension (Vox Implants) must be mentioned [29–32]. The material has the effect of permanent augmentation but stiffens the area of the vocal fold around the injection site. To a certain extent, it may also be applied for correction of the position of the arytenoid cartilage. The material originates from the discipline of urology (UroPlast) and was CE certified for the indication of permanent vocal fold augmentation with the brand name of Vox Implants. Therefore it may be applied in-label. Generally, the widely lateral injection between the thyroid cartilage and the muscles is important in order to avoid stiffening of the vocal fold and to ensure good tissue compatibility (see ▶ **Fig. 3**). To avoid misplacement and to preserve the option to well distribute the biomaterial, the application is recommended to be performed under general anesthesia in the context of microlaryngoscopy.

This alloplastic material is highly biocompatible, non-toxic, and the costs are acceptable in comparison to thyroplasty. Especially for older patients with bronchial or esophageal carcinomas with aspiration disorders, injection laryngoplasty with Vox Implants provides a rapid therapy option. Granulomas as caused by Teflon or severe foreign body reactions provoked by GoreTex are not known with a correct lateral injection. However, the silicone particles induce connective tissue reaction. Smaller quantities may be taken outside the larynx by macrophages and deposited. The connective tissue in the neighborhood of polymethyl dioxane particles may mimic a tumor disease in the FDG-PET examination [33, 34]. In cases of necessary permanent augmentation for patients with curative treated malignant diseases of the larynx, hypopharynx, or thyroid gland, Vox Implants is contraindicated and autologous fat is preferred which can be well differentiated from tumors in MRI and PET-CT scan. If paralysis of the opposite focal fold may occur, Vox Implants should not be applied because the surgical removal of the material is rather difficult.

An intermediate position between injection laryngoplasty and medialization thyroplasty is assumed by the insertion of polytetrafluoroethylene (GoreTex) straps between the thyroid cartilage and the paraglottic muscles for permanent medialization of the vocal fold. This procedure is predominantly applied in the USA. The surgeon individually cuts the straps from a patch manufactured for pericardial reconstruction or vascular surgery and insert it through a small anterior thyroid window [35]. Even an approach from the inferior edge of the thyroid without window has been described [36]. So, it is neither an injection technique in the proper sense of the word, nor a typical thyroplasty. The advantage of this method is the individualized medialization adapted to the patient's needs. Especially the anterior third of the vocal fold can be better aug-

mented. Applications after substance defects of the vocal folds have also been described. These favorable properties, however, are overshadowed by numerous reports about inflammation and rejection reactions requiring the removal of the material in revision surgeries [37, 38]. These experiences have previously also been made at the occasion of the use for camouflage for rhinoplasties [39]. In any case, the material is not CE approved for extracardiovascular applications and the biomaterial that is offered only in large dimensions is very expensive.

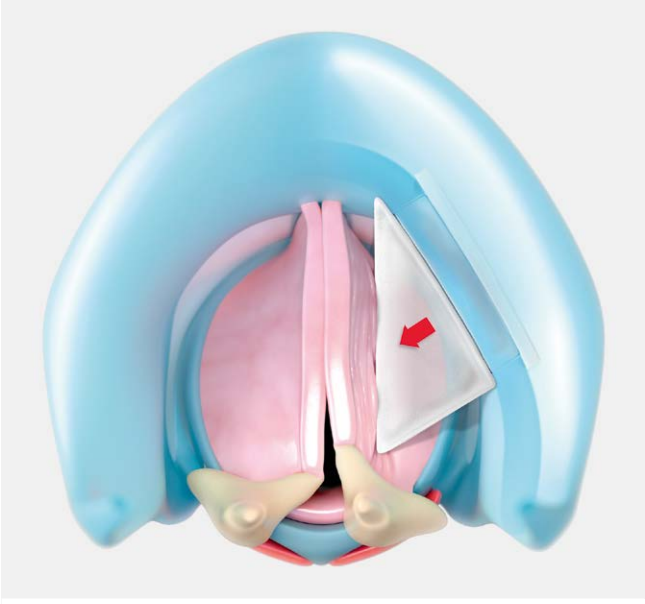
1.2 Medialization laryngoplasty (ML)

The objective of the procedures described here is the permanent medialization of irreversibly paralyzed vocal folds in order to restore the complete glottis closure during phonation. The first description of the term of thyroplasty dates back to 1974 and the classification of phonosurgical interventions at the thyroid cartilage was introduced by Isshiki [40]. He was the first to describe in a dog model the lateral compression of the endolarynx in cases of paralysis by vertical incision of the thyroid cartilage and stepwise inward placement of the posterior two thirds as *thyroplasty type I.* One year later, he published the creation of a thyroid cartilage window in humans on the level of the vocal fold with an autologous thyroid graft [41]. A proposal of a classification made by the European Laryngological Society (ELS) in 2001 summarized the procedures of thyroplasty type I and arytenoid adduction as approximation laryngoplasty [42]. However, this classification could not prevail up to now.

1.2.1 Autologous implants

Already in 1915, Payr described vocal fold medialization with autologous thyroid cartilage [43]. This principle was taken up again and again, in the 1950s by Opheim [44], in the 1970s by Isshiki [41], in the 1980s by Kleinsasser [45], and even currently [46, 47] with several modifications. Beside thyroid cartilage, also the use of rib cartilage [48], nasal septum and ear cartilage [49, 50] have been mentioned while no advantage could be shown in comparison to thyroid cartilage that is available at the surgery site.

The advantages involve the high biocompatibility even in children, the simple resection at the surgery site without additional costs and the certainty that foreign body reactions in subsequent imaging do not cause artifacts. In general, the disadvantages include a limited adjustability due to the given thickness of the cartilage, and risks of dislocation and cartilage resorption decreasing the effect of the thyroplasty. Also, the effect on a posterior gap is limited. The cartilage removal at the upper edge of the thyroid may lead to postoperative hematoma, airway swelling, and swallowing problems. The significant issue of resorption could not yet be clarified satisfactorily. In 1995, Tucker conducted a thyroplasty trial with dogs using autologous thyroid cartilage. Histology after 6 months revealed an acceptable volume loss of 13 %. Other authors report about clinical experience with higher rates. Already Isshiki emphasized the careful use of the tissue and the importance of preserving the perichondrium at the cartilage in order to secure nutrition of the cartilage [51]. Experienced surgeons may still apply this method, especially when patients are reluctant with regard to foreign material for thyroplasty.



▶ **Fig. 4** Principle of medialization thyroplasty (ML) with thyroplasty window creation and silicone wedge (white wedge).

1.2.2 Silicone implants

Already very early, alternatives for autologous cartilage have been investigated for thyroplasty type I. Initially, the cartilage of the thyroplasty window was further used with its perichondrium as stamp; and foreign material was applied for locking and later also for V-shaped adaptation of the medialization effect under auditive control in surgeries performed in local anesthesia [52, 53]. Most widely used are medical silicone blocks that are individually cut during surgery [54]. The advantage consists of the individual shaping with consideration of the sex-specific thyroid angle [55], the length of the thyroid ala, and the malposition of the paralyzed vocal fold that shall be corrected (see ▶ **Fig. 4**). As in all below-mentioned type I thyroplasties, the success depends on the correct size (Koufman formula) [53] and placing of the thyroid cartilage window. To avoid a extrusion of the foreign material into the endolarynx, a too high stamp pressure on the tissue and sharp edges should be avoided. This technique should only be performed by very experienced laryngologists. Only non-reinforced, medical grade silicone blocks should be used as the base material for the intraoperative cutting of these implants.

The advantage of pre-shaped silicone wedges is that measures proven in studies are kept so that insertion may be performed with individually cut implants based on templates [56, 57]. This also includes the pre-shaped, but individually adaptable Netterville PhonoForm silicone blocks [58] that are distributed by Medtronic Company. These products are FDA approved, but not CE certified.

Silastic implants that have been specifically developed for thyroplasty provide a better patient safety since they have round edges and an integrated dislocation protection. They may be chosen in 6 sizes (for males and females each) based on a test stamp range (Montgomery Thyroplasty Implant System) [59, 60]. For this implant, investigations about the biocompatibility are available and they are CE approved so that they may be applied in-label.

1.2.3 Ceramic implants

In 1993, Cummings, Purcell, and Flint developed an implant system for thyroplasty made of hydroxyl apatite in 6 different prefabricated sizes [61]. As of the beginning of the 1990s, hydroxyl apatite became widely distributed as bone graft substitute in medicine and dentistry. The material disposes of good biocompatibility and stability. With this implant, the first-describing authors wanted to imitate the firm cartilage-bone structure of the thyroid cartilage and secure a safe anchoring at the thyroid. Extrusions and postoperative swelling have been described in the introduction phase [62].

Test stamps of 3–8 mm penetration depth may be inserted via a standard thyroplasty window for medialization of the vocal fold. The stamp with the best endoscopically or auditively controlled medialization effect assessed under local anesthesia is chosen as ceramic implant and secured with the according locking clip. The implant system is distributed by Olympus Company under the brand name of VoCom and is CE certified. In Germany, the system is not widely used.

1.2.4 Titanium clips

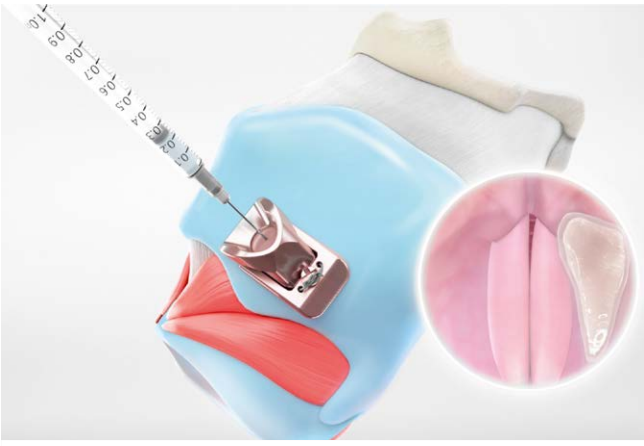
In 1996, Friedrich developed the Titanium Vocal Fold Medializing Implant (TVFMI) in cooperation with Heinz Kurz Company (Dusslingen, Germany) [63]. The clip that is made of medically pure titanium was intended to reduce the time efforts for the surgeons like other pre-shaped implants. It shows a stable mechanical and functional medialization effect [64]. In comparison to silicone implants, titanium clips have better functional results, however, they are not statistically significantly better [65, 66]. The long-term results are stable [67]. For TVFMI as well, single reports about extrusions and dislocations have been published. In Austria and Germany, the system is widely used.

1.2.5 Secondarily adjustable implants

Up to now, none of the described implants could reveal a general superiority over other implants. Considering critically the long-term results of medialization thyroplasty with silicone, ceramic, titanium, and autologous implants, the revision rate in larger trials varies between 5.4 % and 33 % [68, 69]. According to a USA wide survey performed by Rosen [69], the reasons for revision were predominantly the under-correction and/or the decreasing glottic closure (33 %). According to Woo, the remaining glottic insufficiency refers the posterior third with 55 % [70]. In this study, cases with preoperatively severer posterior glottic gap that have already been combined treated initially with arytenoid adduction are not taken into account. Only in 6 % of the cases, the implant had to be replaced with a smaller one due to over-correction [69]. In 8 %, repositioning was necessary [69]. In revision cases, dynamic computed tomography trials in phonation show an under-correction of up to 75 % in thyroplasty, followed by a too high or regarding the vocal fold axis angled position of the implant [71]. Consequently, the exact positioning of the thyroid cartilage window and the individual adaptation of the implant size has a particular significance in order to achieve optimal voice improvement and to avoid revision surgery. The surgical exposition, the exchange or repositioning of thyroplasty implants are associated with higher complication rates with regard to airway obstruction, swallowing disorders, hematoma, and thyroid cartilage stability [72].

Therefore, the wish to develop secondarily adjustable implants for thyroplasty was stated. The first implant of this type was the Thyroprotip titanium implant with an adjusting screw and a stamp made of titanium pearls welded together that should secure the ingrowth of connective tissue and thus an intensive adhesion with the paraglottic soft tissue [73]. With this adjustable implant, it was possible during revision to increase or reduce the stamp effect without removing the anchoring of the implant body in the thyroid cartilage. This method was CE certified. However, the implant, probably due to the takeover of the Protip Company, was not further developed and new results are not available.

Consequently, the approach of secondary adjustability and the securing of optimal window position was recently pursued by Ho et al. [74]. The VOIS Implant in 4 different sizes and the according instrument set for positioning the thyroid cartilage window is a CE approved secondarily adjustable implant system. It combines the advantages of a titanium corpus anchoring in the thyroid that is easy to implement and dislocation-safe with a tissue-friendly silicone pad for individual medialization of the vocal fold. After choosing the appropriate size of the implant based on the sex and the thyroid ala length, the silicone pad can be re-filled with NaCl under endoscopic control according to the necessary stamp effect. Without re-surgery, the micro port located at the outside of the thyroid cartilage may be punctured under ultrasonographic control and the filling volume of the silicone pad may be adjusted in cases of over- or under-correction (see ▶ **Fig. 5**). Another significant advantage of this implant is the vector of the expanding silicone pad. While the flank of the implant medializes the vocal fold, the tip of the silicone pad displaces the vocal process in medio-dorsal direction so that an additional intervention for arytenoid adduction is possibly no longer necessary.



▶ **Fig. 5** Medialization thyroplasty (ML) with effect on the arytenoid position with a secondarily adjustable composite implant (VOIS Implant), the silicone pad that may be refilled with NaCl is depicted in grey.

1.3 Arytenoid adduction and cricothyroid subluxation

Recurrent laryngeal nerve paralysis affects all inner laryngeal muscles of the respective side. Depending on the severity of the damage of the single muscles, the predominant findings consist of vocal

fold bowing due to a damaged thyroarytenoid muscle (TA) or pathologic intermediate or lateral position due to failure of the lateral cricoarytenoid muscle (LCA). The weakness of the posterior cricoarytenoid muscle (PCA) does not only inhibit the opening of the glottis but also reduces the counter-tension at the arytenoid cartilage against the tension of the non-affected cricothyroid muscle (CT). As a consequence, the vocal process is displaced in anterior direction with shortening of the vocal fold. The interarytenoid muscles (IA) getting bilateral innervation. Unilateral paralysis leads to incomplete closure in the area of the posterior commissure, mostly rather due to the anterior-cranial tilting of the arytenoid cartilage (LCA/PCA effect) than due to IA weakness. Recurrent laryngeal nerve paralyses with severe LCA weakness and tilting of the arytenoid cartilage cause an relevant posterior glottis gap that cannot be corrected with standard ML alone. Therefore, Isshiki introduced arytenoid rotation in addition to thyroplasty type I already in 1978 [75]. By means of two non-absorbable threads at the muscular process of the arytenoid cartilage pulling to the anterior inferior edge of the thyroplasty window, he mimicked the effect of the LCA and rotated the vocal process in medio-caudal direction. That is why this procedure is also called arytenoid adduction (AA). A series of modifications were related to the traction direction of the thread to a fixation point that is located even more anterior-medio-caudally below the insertion of the vocal fold at the inferior edge of the thyroid cartilage [76]. Other modifications concerned the position and size of the additional cartilage window at the posterior edge of the thyroid [77] and less invasive approaches to position the thread, e. g., the sling or string pull technique described by Hess [78, 79]. AA is technically more complex, and the combination of ML with AA is associated with a clearly higher risk of hospital re-admission within 30 days [80]. Specific risks of AA are postoperative bleeding, posterior laryngeal swelling with temporary swallowing problems and risk of aspiration, and perforation of the hypopharynx. The surgery is irreversible because the lateral joint capsule is opened for mobilization resulting in a fixation of the cricoarytenoid joint (CAJ). In the context of AA, synkinetic nerve fibers may be transected due to the close neighborhood of the recurrent laryngeal nerve to the CAJ, possible leading to further tension loss and atrophy of the vocal fold.

The additional functional gain by combining ML with AA could only be shown in studies that have performed stratification based on a large posterior glottis gap or high voice-related handicap (VHI) [81]. In all other cases, ML alone could achieve sufficient voice improvement [82]. The definition of a *large* posterior glottis gap is not clear in the literature. According to Yilmaz and Özer, the gap should only be classified as large when the vocal process remains in abduction position during phonation [83].

In 1998, Zeitels et al. introduced a therapeutic option called *Adduction Arytenopexy (AApexy)*[84]. With this procedure, the correct position of the arytenoid should be achieved as in AA and at the same time the length and tension of the vocal fold should be increased. The CAJ is opened more widely, and the muscular process of the arytenoid cartilage is fixed at the cricoid plate after medio-cranio-posterior displacement. This interesting method requires an even more extensive posterior exposition of the larynx and the complication risks become more significant. Due to the complexity of the intervention and the mentioned risks, AApexy could not prevail like the so-called *Cricothyroid Subluxation* that had been introduced by the same team [85]. This procedure consists of opening the cricothyroid joint, and a suture pulls the inferior horn of the thyroid cartilage in anterior direction to the cricoid arch so that the paralyzed vocal fold is tightened.

Apart from AA, an innovative approach for endoscopic correction of the vocal fold position has recently been presented by Rovo et al. [86]. The authors manually reposition the arytenoid cartilage in the context of microlaryngoscopy and fix the position by means of fat injections laterally to the vocal process and the arytenoid body. The long-term results of this method must be awaited.

Unfortunately, the application of AA and the surgical experience with AA in the USA and in Europe is continuously decreasing during the last 10 years [87].

1.4 Other procedures and outlook

Re-innervation of the paretic laryngeal muscles can be done without the use of biomaterials. Already in 1925, Colledge made first successful attempts to anastomose the recurrent laryngeal nerve (RLN) stump with the vagus stem or the phrenic nerve in monkeys [88]. Tucker was the first to describe the nerve-muscle pedicle re-innervation of the PCA in 1976 [89] and in 1977 the re-innervation of the LCA with this method [90]. In 1984, Crumley introduced the concept of selective re-innervation by anastomosing the ansa cervicalis with the RLN adductor terminal branches and phrenic nerve fibers to the RLN abductor branches [91]. These complex and risky surgeries are usually not required in cases of unilateral paralyses. Based on this concept, Crumley described the partial step of anastomosing the ansa cervicalis with the RLN stem as non-selective re-innervation (NSR) in 1988. With this method, the objective of recovered motility of the vocal fold was abandoned. The re-toning and medialization of the paralyzed vocal fold became the primary objective. Thus, this procedure represents an alternative to ML. If implants are not used, foreign body reaction, extrusion, or dislocation can be avoided. Furthermore, the vibrating ability of the vocal fold is not impaired by inserted biomaterials. The functional advantage of NSR that is less known in Europe compared to ML, is currently investigated in a British phase-2 study (VOCALIST) [92]. Our own experience with a modified NSR performed in contrast to Kodama [93] without AA, showed good toning of the vocal fold after 3–4 months. In our method the transection of the RLN that still has a remaining function after synkinetic re-innervation is avoided. An additional adductive innervation to TA/LCA is provided by an ansa-nerve-muscle pedicle inserted via a thyroid cartilage window. In contrast to ML, the position and the tonus of the vocal fold improved further after 12 months and up to 24 months with excellent voice quality [94].

In the future, the neurostimulation of a synkinetically re-innervated TA/LCA complex might provide another alternative for ML in cases of particular voice requirements (e. g. singers, speaking professionals) [95]. Electrical impulses that are delivered synchronously to the adduction of the healthy vocal fold can elicit the contraction of a synkinetically re-innervated vocal fold [96].

The disadvantage of all static medialization techniques of paralyzed vocal folds is the permanent reduction of the glottic gap that becomes a breathing limitation for patients with high respiratory requirements [97, 98]. By means of functional electrical stimulation,

the vocal fold remains in a more favorable position for respiration and is active adducted during phonation.

However, this is still an innovative research approach. In the upcoming years, an approved medical product will probably not be available yet. However, first clinical experiences with neurostimulation in cases of bilateral paralysis (see next chapter) are promising [99, 100].

Another field for research and development regarding the assessment and comparability of the results of surgical procedures in cases of unilateral RLN paralysis is the improvement of the objectiveness and reproducibility of laryngo-stroboscopic findings. Bakhsh et al. could show that the multitude of parameters to describe the vocal fold position or the glottis gap combined with unmatched grading systems make the comparability of the study results more than difficult [101]. Only 7 of 21 investigated laryngo-stroboscopic parameters confirmed obvious postoperative differences compared to the preop condition. Surprisingly, the periodicity and the bowing of the vocal fold were more significant than the glottis gap during phonation. Functional parameters like the maximum phonation time (MPT) or the questionnaire on the voice handicap (VHI) could be reproduced clearly more easily.

2. Bilateral vocal fold paralysis

While the voice quality, especially breathy voice, is considered as most impairing in cases of unilateral vocal fold paralysis, patients affected by bilateral vocal fold paralysis suffer predominantly from the limited air flow through the glottis. Depending on the position and tension of the vocal folds, the complaints range from exercise-induced dyspnea to dyspnea at rest and respiratory insufficiency.

Initially, patients often report about accompanying voice disorders and tendency of aspiration. In the further course of synkinetic re-innervation, that starts with absent functional recovery after 4–6 months, the voice and the aspiration protection become better, the exertional dyspnea, however, increases and forces the patients to accept therapy.

In cases of favorable glottis gap, normal body mass index (BMI), and good respiratory reserve in younger, otherwise healthy patients, the narrow glottis gap may be tolerated if no infection is present. Based on our experience, CPAP therapy at nighttime may be helpful in order to find restorative and low-noise sleep. If at least unilateral restoration of the motility is possible in the context of paralysis that has occurred only few weeks or months ago, the temporary laterofixation of one vocal fold should be considered for severe respiratory problems.

2.1 Laterofixation

Up to the 1980s, tracheostomy was the therapy of choice. Already in 1939, King described an open surgical procedure [102] comprising the opening of the capsule of the CAJ and suture of the mobilized arytenoid cartilage displaced in lateral direction to the thyroid cartilage, similar to orthopedic surgery. In addition, King anastomosed the end of the omohyoid muscle that was detached from the hyoid bone at the muscular process of the arytenoid cartilage. This poorly spread-out method was modified by Schobel [103] (3 sutures at the cricoid cartilage, no muscle transfer) and was frequently applied in Germany in the second half of the 1980s. The disadvantage of open laterofixations was the invasiveness of the procedure with postoperative glottis swelling and maintenance or necessity of tracheostomy. The transition to endoscopic laterofixation by Ejnell [104] and Lichtenberger [105–109] allowed the omission of tracheostomy. While Ejnell exposed the thyroid cartilage from external in a combined intervention and placed cannulas above and below the vocal process, Lichtenberger used a needle carrier that he had specifically developed for this application to pierce from the inside to the outside through the thyroid cartilage, the muscles, and the skin. The result of both techniques is that a non-resorbable thread is pulled over the vocal process and the abutment of the thyroid cartilage. In this way, the lateralization of the arytenoid cartilage and the vocal fold is achieved. These methods are not associated with irreversible opening and subsequent scar-related fixation of the joint. Thus, both procedures may be considered as reversible and can be applied for temporary laterofixation in cases of dyspnea and unclear prognosis. One problem of all pulling techniques for laterofixation is the anterior displacement of the loop over the vocal process due to the antero-lateral pulling direction and with it the possible transection of the vocal fold anteriorly to the vocal process (effect of cutting wire as for cheese or butter). This leads to a decreasing effect of lateralization, the risk of granulations and later scars that may result in permanent voice disorders even after removal of the thread. If the motility recovers on the contralateral or the laterofixed side, the thread may be removed. If the abduction does not reappear within 12 months, the thread may remain in situ. In cases of pains or decreasing effect, the thread should be removed and permanent glottis enlargement is to perform.

If already initially an unfavorable prognosis for abduction recovery on one side must be expected, permanent laterofixation may be performed primarily. This situation may be observed in cases of preexisting paralysis, known (surgery report) or confirmed (EMG) irreversible damage of the RLN, or scar fixation of the CAJ on one side. In the context of permanent endoscopic laterofixation, the thread technique is either combined with an opening of the CAJ and mobilization of the arytenoid cartilage in the sense of arytenoid lateropexy [110] (most suitable for posterior glottis stenoses but also for bilateral paralyses) or with laser surgical glottis enlargement [111]. Significant further development of the laterofixation technique was performed by Rovo et al. [112, 113] from Szeged who developed a set of knives to detach the CAJ capsule and a modified endo-extralaryngeal needle carrier allowing a more dorsal placement of laterofixation. In this way, the risk of displacement of the loop in direction to the middle part of the vocal fold is significantly reduced [114].

2.2 Endoscopic glottis enlargement

Open surgical glottis enlargement may be considered as abandoned since the 1980s because of the necessity of temporary tracheostomy and expectable swallowing disorders. With the option of endoscopic electrocautery for laryngeal bleedings, Thornell was the first to describe endoscopic arytenoidectomy in 1949 [115]. As biomaterial, an acrylic obturator was fixed for 3–4 weeks between the arytenoid cartilages for shaping the glottis enlargement. In 1968, Kleinsasser further developed microlaryngoscopy and combined endoscopic arytenoidectomy with submucous chordec-

tomy of the posterior two third of the vocal fold with sutured wound closure [116]. In the mid-1980s, with introduction of the CO_2 laser in laryngeal surgery, the first laser arytenoidectomies were performed for treatment of bilateral vocal fold paralysis by Lim and Ossoff [117, 118]. This technique was further developed by Remacle et al. [119] in the sense of preservation of the posterior part of the arytenoid cartilage to reduce the risk of aspiration and by Sato et al. [120] with preservation of the medial mucosal covering of the arytenoid cartilage to avoid re-stenoses due to posterior scar formation.

In 1989, Dennis and Kashima described laser chordectomy as partial, C-shaped resection of the medial parts of the vocal fold directly in front of the vocal process and defined the standard therapy of laser surgical glottis enlargement for a long period [121]. Further modifications in terms of more extended paraglottic chordectomy were published by Reker [122] and Eckel [123]. According to the balance between voice and respiration, the procedures were developed on one hand in direction of minimized laser resection [124–127] and on the other hand to more extended laser resections in cases of higher respiratory demands [128, 129] to possibly allow decanulation. A good overview about the variety of procedures for laser surgical glottis enlargement with instructive drawings was published by Sapundzhiev et al. [130].

The primary endpoint of former studies about the described procedures was the decanulation rate. Today, tracheostomy can be avoided in many cases. In comparison to the procedures that may be chosen for endoscopic glottis enlargement, the question of prospectively assessed improvement of respiration with at the same time preservation of a voice quality for everyday situations must be asked. The first comprehensive multicenter trial with prospective design on the outcome of glottis enlargement in Germany was published performed by Nawka et al. [113]. The respiratory and voice function of 36 patients were assessed preoperatively and 6 months after therapy. The treatment was performed according to the standard of the respective center either as posterior chordotomy, partial arytenoidectomy, or laterofixation. In all cases, breathing and the quality of life could be improved. However, in 25 % of the cases, severe respiratory problems occurred that required a second intervention.

The outcome of the voice quality in this study revealed an objective reduction of the maximum phonation time, a reduction of the voice range profile, and an increased hoarseness in all patients whereas patients who had been informed about the risk of poorer voice quality did not perceive the deterioration as very severe [132]. A recent publication of this team including 11 centers in Europe with retrospective data of 326 patients emphasized the variability of the applied methods and the high variance of the results [133]. One third of the patients had undergone tracheostomy before glottis enlargement. One third of them could be decanulated after treatment. 145 of 326 patients needed postoperative cortisone therapy and 58 patients received prolonged intubation after surgery. In 5 % of the cases, surgery did not lead to an improved respiration within 4 weeks and in 3 % not even within 3 months. It is a task for the future to assess the respiratory and voice function in all patients with this rare disease before and after surgery and to limit the treatment methods to the functionally best ones. However, the perioperative swellings remain an unsolved problem in all described procedures and standard operating procedures (SOP) must be elaborated for their management.

2.3 Laryngeal framework surgery (cricoid split)

In pediatric patients, the posterior splitting of the cricoid cartilage with rib cartilage interposition (cricoid split) represents an alternative for enlargement of the glottic gap [134]. This method has been taken from the treatment of pediatric subglottic stenosis and turned out to be suitable for congenital idiopathic bilateral vocal fold abduction paralysis [135–137]. Own experiences confirm that the posterior distance of the vocal folds between the arytenoid cartilages is higher so that the opening triangle can be enlarged. The advantage of this method is the preservation of the CAJ and the muscles that are important for motility (TA, LCA, and PCA). In the context of thorough maneuvers, also the IA muscles may be mostly preserved. Long-term observations show that congenital bilateral vocal fold motility disorders with unclear etiology [138, 139] or assignment to a damage of the first or second motoneuron may recover up to the 10th year of life [140, 141]. Therefore, the cricoid split for decanulation is a useful option with maintenance of the chance of later motility recovery of one or both sides.

2.4 Active implants (laryngeal pacemaker)

The disadvantage of all therapeutic procedures described here is that they are static. By resecting and displacing parts of the vocal fold, the attempt is made to find a balance between facilitated respiration and deteriorated voice to allow the patient to better cope with the life situation. According to all available data, this is only possible to a limited degree. Radical glottis enlargement that had been applied formerly and tracheostomy have certainly improved the respiration, however, they impair the voice-related communication that is nowadays very important in jobs. All careful glottis enlargements with preservation of an acceptable voice quality also make reintegration in society and profession difficult due to the persisting physical restriction. Our experiences with patients who have at least a residual motility of one vocal fold despite bilateral paralysis reveal that they achieve better results regarding respiration and voice.

▶ **Fig. 6** LP system components (laryngeal pacemaker development project of MED-EL company) consisting of a microelectrode for opening stimulation of the posterior crico-arytenoid muscle (PCA), the LP implant with inductive transmission coil, and connectors for 2 electrodes and the external LP processor with control unit and battery.

The objective when further developing therapeutic procedures for bilateral paralyses must include the, at least partial, restoration of the disturbed motility [142]. This is generally possible because most of the patients with permanent bilateral RLN paralysis are not denervated. When comparing muscular atrophy of the shoulder after accessory nerve paralysis with the mainly preserved volume of the paralyzed vocal fold after RLN paralysis one can assume that a relevant part of the muscle fibers must have received re-innervation. Electromyography of the paralyzed laryngeal muscles confirms this hypothesis [143, 144]. Based on the current knowledge, the absence of motility recovery despite re-innervation is explained by a pathological re-innervation with co-activation of agonists and antagonists, comparable to the autoparalysis of the eyelid or the corner of the mouth in cases of facial nerve paralysis [145, 146]. Crumley [147, 148] described the so-called laryngeal synkinesis as typical pathological re-innervation condition where phonation leads to activation of the PCA or sniffing or deep inspiration in the TA results in increased EMG activity. In up to 80 % of all RLN paralyses, synkinetic defect healing occurs [149]. On one hand, the evidence of this synkinetic re-innervation in the EMG deteriorates the prognosis of motility recovery [150]; on the other hand, a synkinetically re-innervated muscle provides the preconditions to be triggered to contraction by electrical neuromuscular stimulation [151]. When the stimulation occurs peripherally in the target muscle, the autoparalysis of the larynx may be overcome and selective opening and closure of one vocal fold may be induced. This is the basic principle of neurostimulation devices like the Laryngeal Pacemaker (LP) System by the company MED-EL, Austria, that will be applied after finalization of clinical trials as LP for the treatment of bilateral vocal fold paralysis in synkinetically re-innervated PCA muscles [99, 100, 152–161].

The idea of a laryngeal pacemaker has already been pursued since the 1970s [162]. After successful testing in animal experiments [163–169], Zealear and Herzon were the first in 1996 to trigger intraoperatively the electrically stimulated vocal fold abduction during thyroplasty by means of an external stimulator in humans [170]. In 2003, Zealear et al. published a first multicenter clinical trial about the application of the Medtronic pain therapy implant named *Itrel II* for larynx reanimation [171]. Due to electrode corrosion and the necessity of switching to monopolar stimulation, no further trials with this implant were conducted.

▶ **Fig. 7** Schematic description of the LP system of MED-EL company in situ with the electrode leading to the posterior crico-arytenoid muscle (PCA) for unilateral stimulation. The implant is fixed subcutaneously on the sternum, the processor is held in its position by means of a magnet on the implant.

With the LP System, an active implant is available that has been specifically developed for bilateral RLN paralysis that combines a minimally invasive and reversible surgical procedure for implantation of microelectrodes with an impulse generator that is adapted to the neurostimulation of laryngeal muscles (see ▶ **Fig. 6**). In a first clinical trial encompassing three centers in Germany and Austria from 2012 to 2014, the effectiveness and patient safety of the system could be shown in 7 patients [100]. It was possible in all participants of this prospective study to induce the intended vocal fold abduction with improvement of the respiratory function immediately from the time of activating the impulse generator without side effects like pain, swallowing or voice disorders. In contrast to conventional glottis enlargement, the therapy with the LP does not lead to deterioration of the pre-therapeutic voice quality [99]. For safety reasons, the study design limited the electrode implantation to one side in this first-in-human trial (see ▶ **Fig. 7**). With this unilateral opening stimulation, a significant improvement of the PEF (peak expiratory flow), the MPT (maximum phonation time), the voice range profile, and the 6MWT (six-minute walk test) was revealed at the endpoint of the trial after 6 months and the PIF (peak inspiratory flow) as well as the SF-36 (quality of life questionnaire) after 12 months of therapy [100]. Up to 24 months after implantation, a follow-up study did not show any deterioration of all investigated parameters [172]. The mechanical stress of the microelectrodes routing via the neck to the larynx that was caused by the swallowing movements of the larynx turned out to be a risk factor for electrode breaks. In 3 of 7 patients, they occurred within 14 months, and in 2 other patients within 53 months. The LP Systems of the remaining two patients are still fully working today (8 years after implantation) and the respiratory function is good. These study results encouraged the manufacturer (MED-EL, Innsbruck, Austria) to continue the development of the LP System. The mechanical properties of the electrodes were basically reworked to make them more resistant to pulling and bending movements. A planned multicenter pivotal trial will include a higher number of participants to test the new electrode design and the further development of the LP System regarding safety and effectiveness in symptomatic patients.

2.5 Selective re-innervation

An alternative of reanimating the vocal fold motility in cases of persisting RLN paralysis is the selective re-innervation of the abductor and adductor muscles of the larynx. This principle that had been established by Crumley [91] for unilateral paralysis was first investigated in animal experiments for bilateral RLN paralysis [173, 174] and further developed consequently in the clinical application by Marie et al. [175, 176]. For this purpose, the C4 root of the left phrenic nerve is anastomosed with a Y-shaped nerve interposition of the great auricular nerve. Both recurrent nerves are transected, and the Y-shaped interposition is used for neurotization of the PCA muscles on the left and the right side. At the same time, the difficult anastomosis of the thyrohyoid branch of the hypoglossal nerve

with the exposed intralaryngeal adductor branch of the RLN is performed bilaterally. To secure the airway and to prevent aspiration, tracheostomy is necessary because a complete denervation is resulting and a swelling risk of a surgery that takes several hours is relevant. The effect onset of re-innervation may be expected between 6 and 9 months after surgery. In an evaluation published by Marie et al. [177], decanulation could be performed in 35 of 40 patients by means of this therapy. In 30 patients, the respiratory parameters were improved. In 27/40 cases, breath-synchronous abduction of the vocal folds could be achieved at least on one side and in 16/40 patients on both sides.

Li et al. reduced this procedure to the anastomosis of the phrenic nerve and achieved a breath-synchronous PCA activation [178, 179]. Due to the missing adductor innervations, however, TA atrophies or co-activation during PCA stimulation (synkinesis) were observed.

Especially for pediatric patients [180] and young adults [181] who have a good nerve regeneration and may well tolerate the complex intervention, this procedure is an important treatment option that is currently applied in centers in France, United Kingdom, and Belgium.

Conclusion

In the treatment of uni- and bilateral recurrent laryngeal nerve paralyses, bioimplants play a significant clinical role. Their application requires deep knowledge about their biocompatibility, material properties, and for some substances also about the resorption rate, effect duration, and approval for application in the larynx. Depending on the prognosis and the duration of the paralysis, temporary or permanent therapies may be suitable. The more invasive and irreversible the planned treatment method is, the more reliable the estimation of the prognosis must be. Other important aspects for the therapy decision are the severity of the functional impairment due to the paralysis, the individual level of suffering, and comorbidities and/or risk factors that might limit more invasive options. A broad range of bioimplants is available and promising new, also active implants might be approved in the near future. Regarding the counceling of patients, these options should be known, and individualized treatment steps should be planned.

Conflict of Interest

The author was involved in clinical studies on the VOIS implant and the LP System and declare that he has no conflict of interest.

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