Glottic insufficiency in patients with vocal fold atrophy with or without sulcus: treatment modalities and outcome

Broek, E.M.J.M. van den

1

General introduction

Insufficient closing of the vocal folds during phonation (glottic insufficiency) in patients with mobile vocal folds is a pathological condition which can lead to varying degrees of dysphonia, vocal fatigue and reduced quality of life. There are several causes of glottic insufficiency. In this thesis we focus on glottic insufficiency caused by vocal fold atrophy and/or sulcus and surgical treatment.

In the last decades surgical treatment options for these pathologies have expanded. There are endoscopic and external medialization procedures using different injection materials and implants. There are microphonosurgical approaches for sulcus using different excision techniques. And more recently the use of techniques from regenerative medicine have been introduced. With all these different surgical treatment modalities to choose from, in addition to variations in the underlying pathology, it is challenging to compare outcome results.

In this thesis, we focus on reporting our treatment outcomes of two surgical modalities: vocal fold injection (VFI) and laryngeal framework surgery (LFS) with bilateral medialization thyroplasty and we compare our results to other surgical techniques. We also investigate the use of outcome measurement instruments (OMIs) in this specific patient group. With our results we hope to attribute to the ultimate goal to identify the best treatment for individual patients with glottic insufficiency caused by vocal fold atrophy and/or sulcus.

In this general introduction causes of glottic insufficiency with mobile vocal folds, overview of surgical treatments and OMIs for voice quality will be further described.

ANATOMY AND PHYSIOLOGY OF THE LARYNX

To be able to understand dysfunction, one must first be familiar with normal function. Anatomy and physiology of the larynx (voice box) will therefore be briefly described.

Anatomy of the larynx

Structurally, the larynx has a cartilaginous framework consisting of the cricoid, thyroid, two arytenoids and epiglottis (Figure 1). The arytenoids are crucial for voicing. They are paired pyramidical cartilages anchored to the posterior lamina of the cricoid through the cricoarytenoid joints. Each arytenoid has a vocal process medially to which the vocal ligament is attached, and a muscular process laterally which is the attachment for the intrinsic laryngeal muscles. Through the cricothyroid joint the arytenoid has a broad reach of movement that involves rotation, sliding and tilting. The movement of the arytenoid and its vocal process outwards - abduction - is important for breathing, and the movement of the arytenoid and its vocal process moving inwards - adduction - is important for voicing (Figure 2). Between the inferior horn of the thyroid and the posterolateral aspect of the cricoid articulates the cricothyroid joint, which allows for a change in angle between the thyroid and cricoid cartilages.

Figure 1. Cartilaginous framework of the larynx

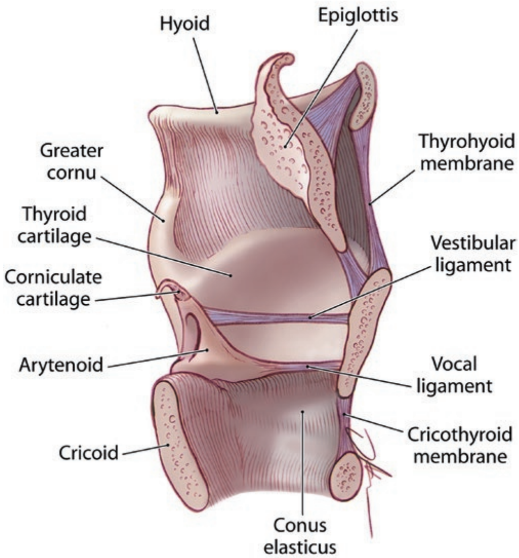


Figure printed with permission [1]

Figure 2. Cricoid, arytenoid, and cricoarytenoid joint; abduction, adduction

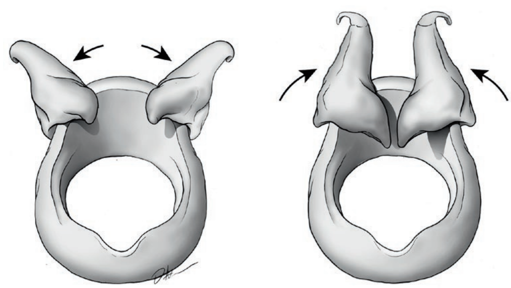


Figure printed with permission [1]

The laryngeal muscles attach to the cartilaginous framework. The extrinsic laryngeal muscles are mostly located on the outside of the larynx and move the framework as a unit upwards and downwards. They include the infrahyoid muscles (sternothyroid, sternohyoid, thyrohyoid and omohyoid muscle) and suprahyoid muscles (mylohyoid, geniohyoid, stylohoid, and digastric muscle) and stylopharyngeus muscle. The intrinsic laryngeal muscles are smaller muscles, mostly located on the inside of the larynx, that move the separate cartilages relative to each other. There are three adducting muscles, the paired lateral cricoarytenoid (LCA) muscles and thyroarytenoid (TA) muscles, and the unpaired interarytenoid (IA) muscle. There is one abducting muscle, the posterior cricoarytenoid (PCA) muscle, and one tensor muscle, the cricothyroid (CT) muscle (Figure 3).

Figure 3. Intrinsic laryngeal muscles and nerve innervation

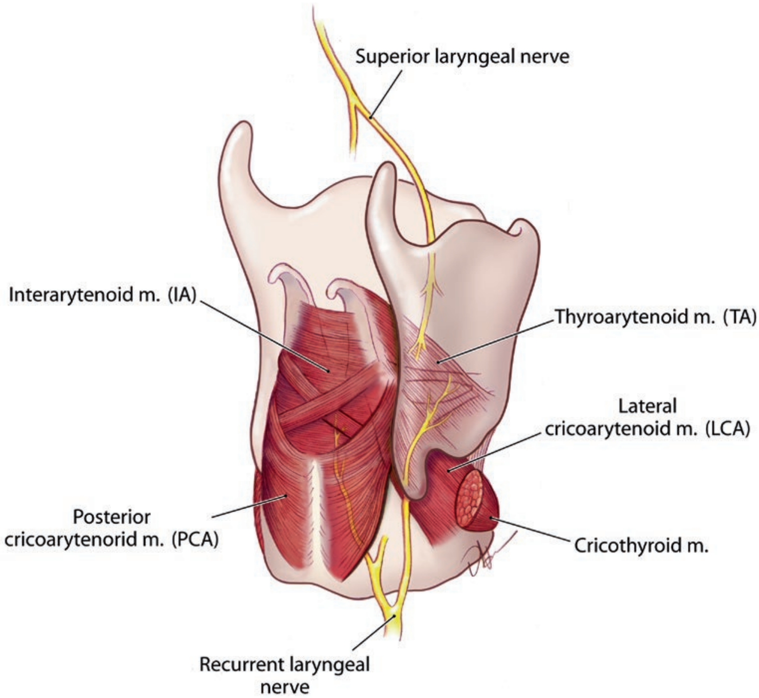


Figure printed with permission [1]

The main nerve responsible for sensory and motor input to the larynx is the vagal nerve (the Xth cranial nerve). It has three major branches: the pharyngeal branch, the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN) (Figure 3). The SLN provides sensatory innervation to the supraglottis and glottis and motor input to the cricothyroid muscle which controls vocal fold lengthening and pitch (falsetto voice). The RLN provides sensatory innervation to the subglottis and innervates all remaining intrinsic laryngeal muscles. If there is no innervation of the RNL this will result in an ipsilateral vocal fold immobility.

Anatomy of the vocal fold

The vocal fold extends from the anterior commissure to the vocal processes of the arytenoid. The true vocal fold consists of multiple (micro)layers. From the surface inwards these are the squamous epithelium, superficial lamina propria (SLP) also known as Reinke's space, intermediate (ILP) and deep lamina propria (DLP) and vocalis muscle (Figure 4). The three layers of the lamina propria - SLP, ILP and DLP - each display increasing rigidity. The SLP is gelatinous with loosely arranged collagen and elastin. In the ILP and DLP the elastin and collagen fibers are more densely organized with the deepest layer (DLP) consisting of tightly arranged collagen fibers. Together the ILP and DLP form the vocal ligament.

Figure 4. Microanatomy of the vocal fold

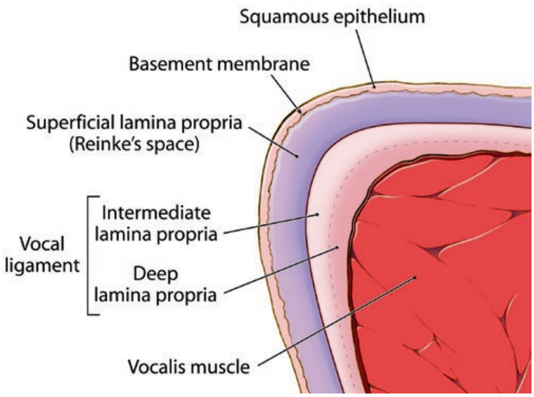


Figure printed with permission [1]

Physiology of the larynx

The larynx is crucial for three basic functions: breathing, swallowing and voicing. The most primitive function of the larynx is to protect the airway; opening of the glottis to breath and closing the glottis to prevent aspiration during swallowing and to allow for airway clearance during coughing. The most complex function is voicing. Voicing is based on two basic physiological principles: (1) closure of the vocal folds followed by (2) vibration of the vocal folds. For vocal fold closure, as described in anatomy of the larynx, innervation, intrinsic laryngeal muscles, arytenoids and cricoarytenoid joints play important roles. Immobility or hypomobility of a vocal fold can be caused by (partial) denervation (neurological) or by fixation of the joint (mechanical).

The second condition for voicing is vibration of the vocal fold. This phenome is described as the glottic cycle, in which short bursts of air are released through the closed vocal folds. These cyclical changes in airflow, amplified by the vocal tract consisting of the pharyngeal wall and oral cavity are what we perceive as voice. In this process the layered microanatomy of the vocal folds (biomechanics) and pressure changes (aerodynamics) come together.

As described the vocal fold consists of layers with different stiffness. This allows the superficial layer (the cover), consisting of epithelium and SLP, to move freely over the deep layers (the body), consisting of the ILP/DLP and muscle. This is known as the body-cover-theory [2]. The underlying force for this movement is the airflow from the lungs passing through the glottis. When vocal folds are closed, the subglottal pressure builds up until it surpasses the holding pressure of the loose, superficial layers of the vocal folds, forcing the cover to move over the body. First the lower lips separate, and as a burst of air passes, the vocal folds separate completely. As airflow continues through the narrow tract between the vocal folds, air pressure will drop (Bernoulli's law) and the lower lip will draw inward and close. As long as phonation is taking place, this glottic cycle will keep on repeating (Figure 5). This fluent "wave-like" movement of superficial layer is called the mucosal wave. A regular mucosal wave will result in a clear voice, but disruption of this wave, by tension variation or disruption of the layered composition, will affect voice quality.

Figure 5. Glottic cycle

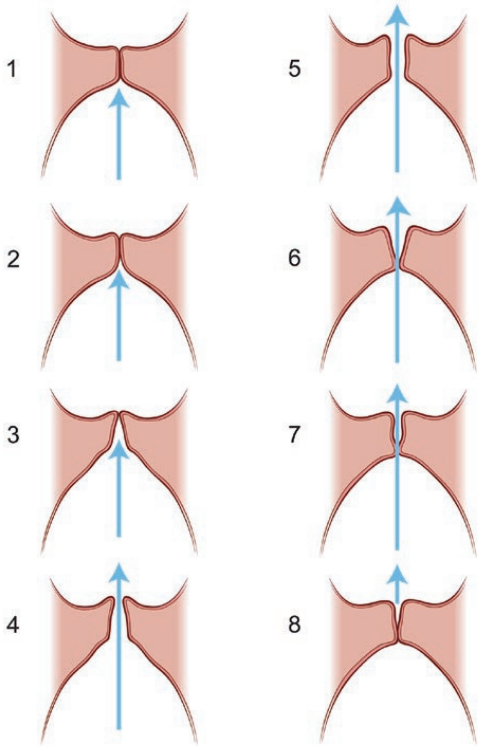


Figure printed with permission [1]

GLOTTIC INSUFFICIENCY

Glottic insufficiency, incomplete closure of the vocal folds, leads to dysphonia. There are several underlying causes, which can be divided into two main categories: glottic insufficiency with unilateral immobile vocal fold or glottic insufficiency with mobile vocal folds. The unilateral vocal paralysis (UVFP) is a well-recognized condition and much has been written about its etiologies and treatment [1]. As this entity is not the subject of this thesis, and the same goes for the unilateral hypomobile vocal fold or vocal fold paresis, they will not be further discussed. This thesis focusses on glottic insufficiency caused by atrophy with or without sulcus in patients with normal mobility of the vocal folds.

Vocal fold atrophy

There are several forms of vocal fold atrophy. A well-known form of vocal fold atrophy is presbylaryngis. It is characterized by atrophy of the lamina propria and the

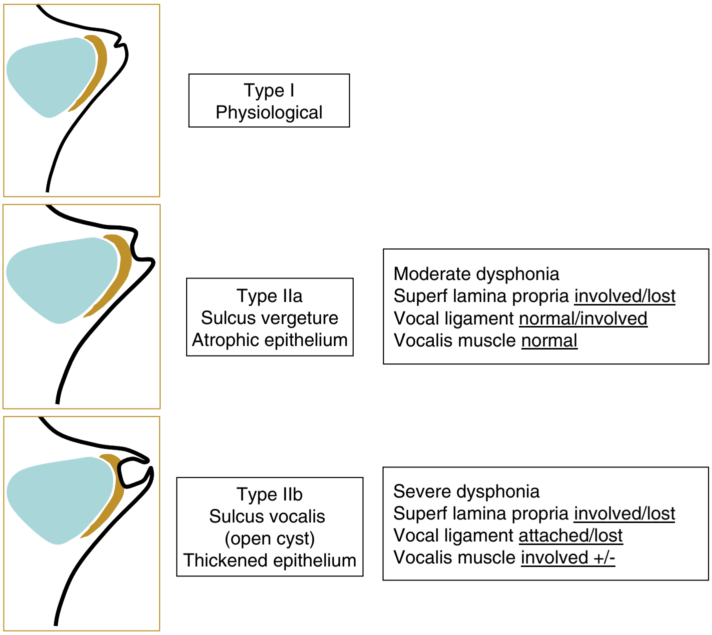
vocal fold muscles, as well as degeneration of the cartilaginous framework due to the aging process [3]. Presbyphonia is the symptomatic dysphonia resulting from presbylaryngis. Voice complaints consist of hoarseness, voice fatigue and difficulty in singing. Clinical evaluation with videolaryngostroboscopy shows bowed vocal folds with incomplete glottic closure and prominence of the vocal processes.
We have also described a form of adolescent atrophy [4]. This is seen in the younger patient population in their 2nd to 4th decade of life with main complaints of hoarseness and vocal fatigue dating back to adolescence. Laryngoscopy shows atrophy of the entire larynx, with wide supraglottic ventricles, a rounded aspect of the anterior commissure and atrophy of the true vocal folds. Interestingly, although encountered regularly at our voice clinic, it has only rarely been described in literature - although some authors have mentioned it [5]. Lastly there is atrophy in combination with sulcus as discussed below.

Sulcus
A sulcus is a groove in the vocal fold running parallel to the free edge. This groove is the result of an invagination of the outer epithelial layer onto the ligament or even onto the vocalis muscle due to atrophy and scaring of the underlying layers. This disturbance of the layered structure will lead to both stiffness and loss of volume of the vocal fold, affecting both closure and mucosal wave. It counteracts the mechanism of the “body and cover” by obstructing the formation of the mucosal wave.

Histologically sulcus vocalis interrupts the superficial layers of the lamina propria on the free edge of the vocal fold with an increase in density of collagen fibers around the sulcus. Sato and Hirano investigated the histopathologic findings of sulcus vocalis under electron microscopy and found sulcus confined to the squamous epithelium and situated in the superficial layer of lamina propria which was thin around the bottom of the sulcus. They found an increased thickness of basement membrane, dense collagenous fibers, decreased elastic fibers in numbers and with altered composition, degeneration of fibroblasts and abnormal fibrogenesis in the macula flava, the cell reservoir of the vocal folds [6].

There are several types of sulcus and these have been described in different classifications. The most used are the classifications according to Bouchayer and Cornut and according to Ford [7,8](Figure 6). Ford type I sulcus is limited to the superficial portion of the lamina propria and is considered physiological with no functional impact. Ford Type IIa sulcus, or a sulcus vergeture according to Bouchayer, is characterized by loss of superficial lamina propria resulting in an area of atrophy with epithelium being attached directly on the vocal ligament. Ford Type IIb, or a sulcus vocalis/open cyst according to Bouchayer, is a narrow invagination of the epithelium extending into the vocal ligament or even into the muscle.

Figure 6. sulcus classification (figure printed with permission [9])



Two different scenarios regarding the etiology of sulcus have been described [9]. First is the congenital origin as postulated by Bouchayer and Cornut. They propose that a sulcus is the result of a ruptured epidermoid cyst originating from the fourth or sixth branchial arch. To support their hypothesis, they used the following findings: early onset of dysphonia in childhood, absence of recurrence after excision, existence of familial cases [7]. The other scenario is that sulcus is acquired due to local trauma and/or chronic inflammatory processes. It may be well possible that congenital and acquired etiologies are complementary [9]. Contrary to sulcus, vocal fold scar is always acquired, most often after laryngeal surgery (iatrogenic), but also after trauma or chronic inflammation as reflux, smoking, or radiotherapy.

Dysphonia in patients with sulci can vary from limited to severe, including hoarseness, strain, voice fatigue and loss of voice control. Both glottic closure and mucosal wave are impaired; there is incomplete closure because of atrophy and tissue loss caused by sulcus and mucosal wave is interrupted by the fibrosis and interruptions in the lamina propria caused by sulcus. Videolaryngostroboscopy can be used for clinical evaluation of these patients, but the sulcus is not always visible which makes it challenging to diagnose. Other findings on laryngostroboscopy can be vocal fold bowing, compensatory hypertonia of the false vocal folds or associated lesions such as hypervascularity or oedema. For definite diagnosis close inspection by in-office endoscopy or suspension laryngoscopy in operating room is often needed.

THE CONCEPT OF SURGICAL TREATMENT

The treatment of glottic insufficiency caused by atrophy and/or sulcus is challenging. On the one hand, vocal fold closure needs to be corrected and on the other hand, mucosal wave needs restoring and rebuilding. This "double pathology" of atrophy/thinning of the vocal folds, but also disrupted layered structure, is more outspoken in sulcus. When treating this pathology, one has the conceptual choice of focusing on improving closure or focusing on improving vibration and mucosal wave.

Improving closure by reducing the glottic gap can be done in a procedure that approximates the vocal folds, a so-called medialization procedure. The techniques are mostly the same as in glottic insufficiency caused by UVFP, but obtaining optimal results can be more difficult in patients with mobile vocal folds.

Correction of the interrupted layered structure of the vocal fold is one of the greater challenges in laryngology. The difficulty is to find surgical techniques that (1) restore the delicate layered structure of the vocal fold and (2) replace the missing lamina propria. Many different surgical procedures have been developed and described, but series are usually small and consisting of mixed pathologies, and outcomes are not reported uniformly. New solutions are continuously being sought, for instance in the field of regenerative medicine, but unfortunately the "perfect" surgical technique has yet to be found. These constraints make it difficult to compare treatments and to decide which modalities are the most effective.

These challenges are discussed in the European Laryngological Society (ELS) consensus statement on vocal fold scarring, which states to always start with the least traumatizing procedure whenever possible, because of the unpredictability of the results of the surgical intervention. From the surgical perspective, optimizing closure is less traumatizing than improving vibration and therefor the consensus statement advices to first consider VFI techniques using a re-absorbable material.

They also emphasize that an optimal result does not only require a skilled surgeon with a broad armamentarium of surgical techniques and procedures, but also a multidisciplinary treatment approach with combining of various (non-)surgical methods [10].

SURGICAL TECHNIQUES

Management of patients with atrophy and/or sulcus can vary from no treatment to speech language therapy (SLT) and surgical procedures often in combination with each other. This introduction gives a short overview of surgical treatment options. As already mentioned, treatment can be divided in (1) medialization procedures to improve glottic closure (2) microphonosurgical procedures to improve mucosal wave by removing/replacing disrupted tissue in case of sulcus and (3) surgery using techniques from regenerative medicine. These different options can also be used in combination.

MEDIALIZATION PROCEDURES

Vocal fold injection

There is a long history of vocal fold injection, with the first injection performed and described by Brünings in 1911 using a self-shaped syringe, the now well-known Brünings' syringe, with paraffin as the injection material [11]. At present there are several techniques for VFI with a variety of injection materials or "fillers". Procedures are performed both in general anesthesia and in-office for a range of indications from UVFP to sulcus. Injectables can be classified based on historical use, material (alloplastic, autologous, xenogenic) and lifespan. In the past, several permanent alloplastic injectables have been used such as Teflon® and silicon (polydimethylsiloxane, PDMS, Vox Implant®). With current knowledge that some of these permanent, inert materials can cause local inflammation with granulation and with the availability of more forgiving alternatives, they are now considered to be obsolete or are used sparingly [12]. Historically, a range of temporary injectables have been available both short and longer term acting. Short-term injectables that have been used in the past are bovine gelatine (Gelfoam, Surgifoam) and bovine collagen (Zyplast), both with a lifespan of about one month. Homologous collagen (Cosmoplast®, Cosmoderm® and Micronized Acellular Derma Compound (Cymetra®) with a longer lifespan of 6-9 months have also frequently been utilized.

Nowadays injectables are easier to use, are available in a variety of consistencies, have a far smaller risk of allergic reactions and don't need skin testing. In the short-term range there are the hyaluronic acid gels (Juvederm ®, Restylane®) and the sodium carboxymethylcellulose gels (Radiesse voice gel®, Renu voice gel®, Prolaryn gel®) with a lifespan from weeks up to several months [1,12]. In the mid to long-term range there are calciumhydroxylapatite (CaHa) compounds (Radiesse®, Renu®, Prolaryn plus®) in addition to autologous fat, both with a lifespan from 9-18 months [1]. In the studies in this thesis, hyaluronic acid is used as a temporary injectable for trial VFI, and autologous abdominal fat harvested with liposuction as a long-term injectable.

VFI under general anesthesia is performed with the patient in larynx suspension and the vocal folds visualized through a microscope or alternatively through an endoscope. Injection of the material is performed using a syringe for which various options are available. The preferred injection site is lateral in the thyroarytenoid muscle at a level of the vocal process. Depending on the material used, specific preparation can be necessary, for example liposuction and preparation of autologous fat. Some degree of overcorrection is needed to compensate for early absorption of carrier materials, but the amount varies between injectables, vocal fold pathology, and preference of the performing surgeon.

Thyroplasty

Thyroplasty was first described by Isshiki in 1975 for UVFP and atrophy [13]. Over time this technique has been used for glottic insufficiency in patients with mobile vocal folds [14]. Modulations have been introduced such as bilateral medialization thyroplasty with Gore-tex® (GORE-TEX® Soft Tissue Patch, Gore Medical, Flagstaff, Arizona) as described by McCulloch [15]. The main surgical steps during thyroplasty with Gore-tex® are (1) positioning of the cartilage window at the level of the vocal fold and (2) adequate medialization, including overcorrection, of the vocal fold by placing the Gore-tex® implant through the cartilage window into the paraglottic space. The advantage of using Gore-tex®, which is a malleable material, is that suboptimal window position can be partly corrected with manipulation of the material within the paraglottic space. Finding the ideal amount of medialization, including overcorrection, is the most challenging aspect of the surgery. Because the patient is awake, she/he can vocalize perioperatively and the surgeon can therefore determine the optimal amount of implant based on perceptual and videolaryngoscopic findings, patient feedback and surgeon's own experience.

MICROPHONOSURGICAL PROCEDURES

In case of sulcus, procedures improving mucosal wave by freeing the epithelium lining and restoring the subepithelial space can be used.

Microphonosurgery: flap with/or without grafting

The main principal in microphonosurgery for sulcus is to improve voicing, by restoring mucosal wave, by repairing the layered structure of the vocal fold. Ideally, this means rebuilding the transitional layer formed by the superficial lamina propria between the epithelium ("cover"), and the vocal ligament ("body"). There are several techniques to free the epithelium and to remove disrupted tissue. The technique broadly used by laryngologists is the formation of the microflap followed by excision of the subepithelial fibrosis and repositioning of the flap with tissue glue or sutures [16,17,18]. A more aggressive form of epithelium freeing is the slicing technique described by Pontes et al. making transvers incisions through the epithelium into the muscle to interrupt the longitudinal fibrosis [19].

Many implant materials have been used to restore the superficial lamina propria. Examples are fibrin glue, gelatine sponge, subepithelial fat graft and subepithelial fascia graft of which the last has been the most reported in the literature [10,20-26].

Angiolytic lasers

A newer technique that has been described is the use of angiolytic lasers, PDL (pulse dye laser) and KTP (potassium-titanyl phosphate), for softening of fibrosis. The use of these lasers was first described by Mortensen et al. in 2008, but also by others [27,28,29]. The working mechanism of angiolytic lasers is based on the concept of selective photothermolysis. The light is selectively absorbed by hemoglobin leading to photocoagulation of microvascular lesions with minimal damage to surrounding tissues, supposedly resulting in softening of fibrosis, leading to more pliable vocal folds, improvement of mucosal wave and, ultimately, improving of voicing [10,28]. Although lasers, as pulsed dye lasers, have shown to be effective for scar treatment f.e. in skin, the mechanism has not been fully elucidated yet. Photothermolysis, but also neo-collagenesis, a process of collagen fiber heating and realignment, have been proposed [28].

TECHNIQUES FROM REGENERATIVE MEDICINE

In the last decade, there has been increasing interest in regenerative medicine for treating vocal fold atrophy, sulcus and scar, because these techniques may have the potential to rebuild and restore vocal fold structure. Regenerative medicine is an umbrella term for techniques that use growth factors, stem cell techniques and scaffolding systems, often in combination. Combining all three techniques is referred to as tissue engineering [30].

For growth factors, the most used is basic fibroplast growth factor (bFGF) [31-35]. Basic FGF stimulates fibroblast proliferation and modulation. Fibroblasts are responsible for maintaining the extracellular matrix (ECM), including the endogenous production of hyaluronic acid, reducing collagen depositions and increasing matrix metalloproteinase (MMP)(collagenase). In 2021 Hirano et al. published a serie of 100 human cases treated with intracordal injection of bFGF [31].

The implantation of stem cells, such as adipose-derived mesenchymal stem cells or bone marrow-derived mesenchymal stem cells, with or without growth factors, may be another approach. Stem cell trials have been mainly performed in animals and an overview of this topic has been giving by Svistushkin et al. [36]. There are only a spare some numbers of human clinical trials [37,38,39]. Future directives for the treatment of vocal fold scarring and atrophy using regenerative medicine techniques will focus on optimizing ECM restoration, retaining longer lasting effects and, ultimately, replacing the entire cover layer.

OUTCOME MEASUREMENT INSTRUMENTS FOR DYSPHONIA

In this thesis we present and compare different surgical treatment outcomes, but to be able to meaningfully reflect on outcome, it is even so important to compare and reflect on the outcome measurement instruments themselves.

Outcome measurement instruments are tools to measure quality or quantity of outcome. An OMI can be a single question, a questionnaire, a score obtained through physical examination, a laboratory measurement, a score obtained through observation of an image, etc.[40]. OMIs are helpful to monitor outcome before and after treatment for patients and health professionals. Monitoring treatment outcome is not only important for the individual patient, but also for a cohort of patients. It can be used for scientific purpose, but also for public and political decision making within our health care system, which is increasingly based on the principles of evidence-based and value-based medicine.

In a consensus statement on the functional assessment of dysphonia, published in 2001 by the European Laryngological Society and recently updated in 2023, authors proposed that the OMIs used for dysphonic patients are divided into five categories. These are subjective, perceptual, aerodynamic, acoustic and videolaryngostroboscopic evaluation [41,42].

Subjective evaluation can be measured with self-assessment tools. Frequently used questionnaires for dysphonia are the Voice Handicap Index (VHI) and Voice related Quality of Life (VRQOL), which both have reasonable good psychometric properties [43–46]. There are also questionnaires developed specifically for glottic insufficiency such as the glottal function index (GFI)[47], the Vocal Fatigue Index (VFI) [48] and the Vocal Fatigue Handicap Questionnaire (VFHQ) [49].

Perceptual evaluation is done by listening to and grading of the dysphonic voice. A widely used scale for this purpose is the GRBAS scale proposed by Hirano in which the dysphonic voice is evaluated in the domains of overall grade, roughness, breathiness, asthenia, and strain [50]. Another voice evaluation tool is the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V), which evaluates the grade of dysphonia, including roughness, breathiness and strain, but also pitch and loudness (Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) Special Interest Division 3, Voice and Voice Disorders. Available at: http://www.asha.org. Accessed June 18, 2010).

Aerodynamic parameters include the maximum phonation time (MPT) in seconds, phonation quotient (PQ) (vital capacity (ml)/MPT (s)), and mean airflow rate (MFR (ml/s)) [41]. Acoustic parameters are jitter (perturbation of frequency), shimmer (perturbation of amplitude) and fundamental frequency (F0), including F0-range (highest to lowest frequency) and softest intensity.

The highest frequency and softest intensity seem to be the most sensitive to changes in voice quality [41]. The use of these parameters depends on the availability of measuring equipment. A pneumotachograph (Phonatory Aerodynamic System (PAS), KayPENTAX, Montvale, NJ) is needed to measure MFR, but also to measure subglottic pressure and aerodynamic resistance. If no pneumotachograph is available PQ can be used as an alternative to MFR.

For acoustic parameters voice program software is needed. These programs are commercially available, for example PRAAT or MDVP (multidimensional voice program software, Computerized Speech Laboratory (KayPENTAX, Montvale, NJ)). These voice programs have their own extensive sets of parameters, often visualized in a phonetogram, from which parameters can be extracted or calculated.

Videolaryngostroboscopy is a standard investigation in dysphonic patients. The two most important aspects are glottal closure and mucosal wave; the last can be assessed for regularity, symmetry and quality, as stated in the ELS-protocol [41]. Comprehensive rating system for assessing videostroboscopy in a systematic and detailed manner have been developed. One example is the VALI (Voice-Vibratory Assessment with Laryngeal Imaging) [51]. For glottic insufficiency there are also specific videolaryngostroboscopic assessment tools, for instance Frame-by-frame analysis (FBFA) in which subject's average percentage of closed frames per glottic cycle is recorded [52].

The ELS protocol was formulated for general dysphonic patients. This may be a limitation when used in a specific population of patients. Therefor Core Outcome Sets (COSs) are being developed for specific conditions [53]. There is no COS yet for patients with glottic insufficiency due to atrophy with or without sulcus.

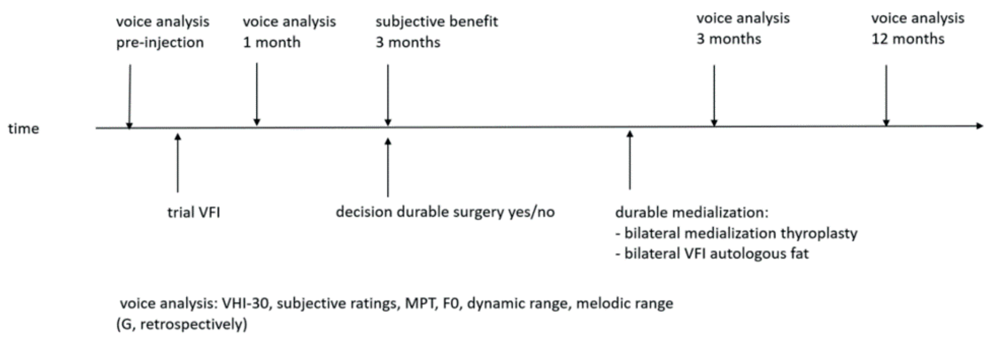
THESIS OUTLINE

LUMC strategy

From 2012, based on the ELS consensus statement [10], all patients presenting at the LUMC (Leiden University Medical Center) with glottic incompetence due to atrophy or atrophy with sulcus have been treated according to the concept of primary correction of closure with a predetermined scheme and timeline with collection of voice outcome data at pre-established time points according to a set prospective protocol.

According to this treatment scheme, patients were offered trial VFI with hyaluronic acid (HA). Voice date were collected preoperative and 1 month postoperative. At 3 months postoperative patients' subjective outcome was evaluated and patients were asked whether they experienced enough benefit from trial VFI to continue to a more durable form of surgery. If yes, patients underwent either VFI with autologous fat or bilateral medialization thyroplasty, depending on patient's and surgeon's preference. Preoperative, 3- and 12-month postoperative voice data were collected (Figure 7). If patients benefit from trial injection was insufficient, they were offered possible other treatment options (microphonosurgery, corticosteroid injections, additional voice therapy) or no further treatment.

Figure 7. timeline treatment glottic insufficiency with mobile vocal folds



The protocol included patients' self-assessment using the VHI-30. In the Dutch version of the VHI-30, a score of 15 points or more identifies patients with voice problems in daily life, a change in pre- and postoperative score of 10 points or more in the individual patient and 15 points or more for a group can be considered clinically relevant [54,55]. In addition, a subjective 10-point rating scale on four domains (quality of voice, effort of voicing, possibility or limitation in voicing, voice influence on life) was collected.

Patient's phonetogram was recorded with the Voice profiler ((Alphatron, Rotterdam, the Netherlands, 2007) in standardized settings. Fundamental frequency (F0, hertz (Hz)) and melodic range (MR, semitones (ST)) were extracted as acoustic outcome measurements. For aerodynamic outcome dynamic range (DR, decibel (dB)) was extracted. Maximum phonation time (MPT) was measured on /a/ at a comfortable pitch and loudness, using the longest MPT from 2 attempts.

For perceptual outcome voices were retrospectively rated by experienced listeners, using the overall grade score of the GRBAS. The cohort of patients treated in this scheme and timeline have been analyzed for this thesis.

Thesis outline

This is a thesis on glottic insufficiency caused by vocal fold atrophy and/or sulcus and the outcome after surgical treatment. We will focus on (1) patient selection, (2) surgical treatment, and (3) outcome measurements.

Chapter 2 shows voice outcome after trial VFI with hyaluronic acid, retrospectively analyzed from data collected according to a prospectively administered voice outcome protocol. It also describes the clinical relevance of trial VFI and the predictive value of trial VFI on the outcome of durable medialization procedure. Chapter 3 reports on voice outcome 3 and 12 months after VFI with autologous fat. Outcome parameters are subjective VHI-30 scores, perceptual evaluation (grade (G)), aerodynamic evaluation, including MPT and dynamic range, and acoustic analysis, including F0 and melodic range. Chapter 4 evaluates voice outcome 3 and 12 months after bilateral medialization thyroplasty with Gore-tex® using the same study design and outcome parameters as in chapter 3. Chapter 5 retrospectively describes the long-term outcome (> 1 year, median follow-up 6.7 years) after bilateral medialization thyroplasty. Chapter 6 contains a systematic review of OMIs for treatment outcome, both surgical and non-surgical, in patients with atrophy and/or sulcus. Strengths and weaknesses of the most frequent used OMIs are discussed. This review may be a first step in developing a COS. In chapter 7, general discussion, we reflect on the importance of using appropriate OMIs and how to define them and we reflect on the surgical techniques investigated in this thesis, discussing future improvements and treatment options for patients with glottic insufficiency caused by vocal fold atrophy with or without sulcus.

REFERENCES

1. Rosen C (2008) Operative techniques in laryngology. Springer-Verlag Berlin, Heidelberg
2. Hirano M (1974) Morphological structure of the vocal cord as a vibrator and its variations. Folia Phoniatr 26(2):89-94
3. Gartner-Schmidt J, Rosen C (2011) Treatment success for age-related vocal fold atrophy. Laryngoscope 121(3):585-589
4. Van den Broek EMJM, Heijnen BJ, Hendriksma M, Langeveld APM, van Benthem PPG, Sjögren EV (2019) Bilateral trial vocal fold injection with hyaluronic acid in patients with vocal fold atrophy with or without sulcus. Eur Arch Otorhinolaryngology 276(5):1413-1422
5. Lindestad PÅ, Hertegård S (1994) Spindle-shaped glottal insufficiency with and without sulcus vocalis: a retrospective study. Ann Otol Rhinol Laryngol 103(7):547-553
6. Sato K, Hirano M (1998) Electron microscopic investigation of sulcus vocalis. Ann Otol Rhinol Laryngol 107(1):56–60
7. Bouchayer M, Cornut G, Witzig E, Loire R, Roch JB, Bastian RW (1985) Epidermoid cysts, sulci, and mucosal bridges of the true vocal cord: a report of 157 cases. Laryngoscope 95(9 Pt 1):1087-94
8. Ford CN, Khidr Al, Bless DM, Gilchrist KW (1996) Sulcus vocalis: a rational analytical approach to diagnosis and management. Ann Otol Rhinol Laryngol 105(3):189-200
9. Giovanni A, Chanteret C, Lagier A (2007) Sulcus vocalis: A review. Eur Arch Otorhinolaryngol 264(4):337-344
10. Friedrich G, Dikkers FG, Arens C, Remacle M, Hess M, Giovanni A, Duflo S, Hantzakos A, Bachy V, Gugatschka M (2013) Vocal fold scars: current concepts and future directions. Consensus report of the Phonosurgery Committee of the European Laryngological Society. Eur Arch of Oto-rhino-laryngol 270(9):2491-2507
11. Brunings W (1911) Uber eine neue Behandelungsmethode der Rekurrenslamung Verhandl. Ver Deutsch Laryngol 18:93–98
12. Lee BJ, Kwon TK, Rosen CA (2021) Vocal Fold Injection. Springer Nature Singapore Pte Ltd
13. Isshiki N, Okamura H, Ishikawa T (1975) Thyroplasty type I (lateral compression) for dysphonia due to vocal cord paralysis or atrophy. Acta Otolaryngol 80(5):465-473
14. Isshiki N, Shoji K, Kojima H, Hirano S (1996) Vocal fold atrophy and its surgical treatment. Ann Otol Rhinol Laryngol 105(3):182-188
15. McCulloch TM, Hoffman HT (1998) Medialization laryngoplasty with expanded polytetrafluoroethylene. Surgical technique and preliminary results. Ann Otol Rhinol Laryngol 107(5 Pt 1):427-432
16. Andreadis K, Hoffman K, D'Angelo D, Sulica L (2020) Sulcus vocalis: results of excision without reconstruction. Laryngoscope 130(9):2208-2212
17. González-Herranz R, Amarillo E, Hernández-García E, et al (2017) Amplitude of glottal mucosal wave after vocal fold microflap with or without fibrin glue. J Voice 31(3):342-346
18. Yilmaz T (2012) Sulcus vocalis: excision, primary suture and medialization laryngoplasty: personal experience with 44 cases. Eur Arch Otorhinolaryngol 269(11):2381-2389
19. Pontes P, Behlau M (2010) Sulcus mucosal slicing technique. Curr Opin Otolaryngol Head Neck Surg 18(6):512-520
20. Campos G, Mantilla N, Ospina JA (2014) Microsurgical release of the cover and fibrin glue implantation for treatment of sulcus and scars. Otolaryngol Head Neck Surg (United States) 151:P73
21. Zhang F, Sprecher AJ, Wei C, Jiang JJ (2010) Implantation of gelatin sponge combined with injection of autologous fat for sulcus vocalis. Otolaryngol Head Neck Surg 143(2):198-203
22. Cantarella G, Mazzola RF, Gaffuri M, Iofrida E, Biondetti P, Forzenigo LV, Pignataro L, Torretta S (2018) Structural fat grafting to improve outcomes of vocal folds' fat augmentation: long-term results. Otolaryngol Head Neck Surg 158(1):135-143

23. Pinto JA, da Silva Freitas MLA, Carpes AF, Zimath P, Marquis V, Godoy L (2007) Autologous grafts for treatment of vocal sulcus and atrophy. Otolaryngol Head Neck Surg 137(5):785-791
24. Karle WE, Helman SN, Cooper A, Zhang Y, Pitman MJ (2018) Temporalis fascia transplantation for sulcus vocalis and vocal fold Scar: long-term outcomes. Ann Otol Rhinol Laryngol 127(4):223-228
25. Pitman MJ, Rubino SM, Cooper AL (2014) Temporalis fascia transplant for vocal fold scar and sulcus vocalis. Laryngoscope 124(7):1653-1658
26. Tsunoda K, Kondou K, Kaga K, Niimi S, Baer T, Nishiyama K, Hirose H (2005) Autologous transplantation of fascia into the vocal fold: long-term result of type-1 transplantation and the future. Laryngoscope 115(12 Pt 2 Suppl 108):1-10
27. Mortensen MM, Woo P, Ivey C, Thompson C, Carroll L, Altman K (2008) The use of the pulse dye laser in the treatment of vocal fold scar: a preliminary study. Laryngoscope 118(10):1884-1888
28. Hwang CS, Lee HJ, Ha JG, Cho CI, Kim NH, Hong HJ, Choi HS (2013) Use of pulsed dye laser in the treatment of sulcus vocalis. Otolaryngol Head Neck Surgery 148(5):804-809
29. Park YM, Lim JY, Kang MS, Choi HS (2019) Treatment outcomes of angiolytic laser-assisted glottoplasty in patients with sulcus vocalis. Ann Otol Rhinol Laryngol 128(5):377-383
30. Fishman JM, Long J, Gugatschka M, De Coppi P, Hirano S, Hertegard S, Thibeault SL, Birchall MA (2016) Stem cell approaches for vocal fold regeneration. Laryngoscope 126(8):1865-1870
31. Hirano S, Sugiyama Y, Kaneko M, Mukudai S, Fuse S, Hashimoto K (2021) Intracordal injection of basic fibroblast growth factor in 100 cases of vocal fold atrophy and scar. Laryngoscope 131(9):2059-2064
32. Miura R, Matsuzaki H, Suzuki H, Makiyama K, Oshima T (2021) Effect of a single injection of basic fibroblast growth factor into the vocal folds: a 36-month clinical study. J voice 37(3):444-451
33. Okui A, Konomi U, Kanazawa T, Komazawa D, Nakamura K, Matsushima K, Watanabe Y (2020) Therapeutic efficacy of basic fibroblast growth factor in patients with vocal fold atrophy. Laryngoscope 130(12):2847-2852
34. Sueyoshi S, Umeno H, Kurita T, Fukahori M, Chitose SI (2021) Long-term outcomes of basic fibroblast growth factor treatments in patients with vocal fold scarring, aged vocal fold, and sulcus vocalis. Auris Nasus Larynx 48(5):949-955
35. Takeharu K, Kurakami K, Konomi U, Komazawa D, Misawa K, Imayoshi S, Watanabe Y (2018) Safety and short-term outcomes of basic fibroblast growth factor injection for sulcus vocalis. Acta Otolaryngol 138(11):1014-1019
36. Svistushkin MV, Kotova S, Shpichka A, Starostina S, Shekhter A, Bikmulina P et al (2022) Stem cell therapy for vocal fold regeneration after scarring: a review of experimental approaches. Stem Cell Res Ther 13(1):176
37. Hertegård S, Nagubothu SR, Malmström E, LeBlanc K (2020) Treatment of vocal fold scarring with autologous bone marrow-derived human mesenchymal stromal cells-first phase I/II human clinical study. Stem Cell Res Ther 11(1):128
38. Ma Y, Long J, Amin MR, Branski RC, Damrose EJ, Sung CK, Achlatis S, Kearney A, Chhetri DK (2020) Autologous fibroblasts for vocal scars and age-related atrophy: a randomized clinical trial. Laryngoscope 130(11):2650-2658
39. Mattei A, Bertrand B, Jouve E, Blaise T, Philandrianos C, Grimaud F, et al (2020) Feasibility of first injection of autologous adipose tissue-derived stromal vascular fraction in human scarred vocal folds: a nonrandomized controlled trial. JAMA Otolaryngol Head Neck Surg 146(4):355-363
40. Prinsen CAC, Vohra S, Rose MR, Boers M, Tugwell P, Clarke M, Williamson PR, Terwee CB (2016) How to select outcome measurement instruments for outcomes included in a “Core Outcome Set” - a practical guideline. Trials 17(1):449
41. Dejonckere PH, Bradley P, Clemente P, Cornut G, Crevier-Buchman L, Friedrich G, van de Heyning P, Remacle M, Woisard V (2001) A basic protocol for functional assessment of voice pathology, especially for investigating

the efficacy of (phonosurgical) treatments and evaluating new assessment techniques. Guideline elaborated by the Committee on Phoniatrics of the European Laryngolo. Eur Arch Otorhinolaryngol 258(2):77-82
42. Lechien JR, Geneid A, Bohlender JE, Cantarella G, Avellaneda JC, Desuter G et al. (2023) Consensus for voice quality assessment in clinical practice: guidelines of the European Laryngological Society and Union of the European Phoniatricians. Eur Arch Otorhinolaryngol 280(12):5459-5473
43. Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G, Benninger MS, Newman GW (1997) The Voice Handicap Index (VHI). Am J Speech Lang Pathol 6(3):66-70
44. Hogikyan ND, Sethuraman G (1999) Validation of an instrument to measure voice-related quality of life (V-RQOL). J Voice 13(4):557-569
45. Francis DO, Daniero JJ, Hovis KL, Sathe N, Jacobson B, Penson DF, Feurer ID, McPheeters ML (2017) Voice-related patient-reported outcome measures: a systematic review of instrument development and validation. J Speech Lang Hear Res 60(1):62-88
46. Speyer R, Kim J-H, Doma K, Chen YW, Denman D, Phyland D, Parsons L, Cordier R (2019) Measurement properties of self-report questionnaires on health-related quality of life and functional health status in dysphonia: a systematic review using the COSMIN taxonomy. Qual Life Res 28(2):283-296
47. Bach KK, Belafsky PC, Wasylik K, Postma GN, Koufman JA (2005) Validity and reliability of the glottal function index. Arch Otolaryngol Head Neck Surg 131(11):961-964
48. Nanjundeswaran C, Jacobson BH, Gartner-Schmidt J, Verdolini Abbott K (2015) Vocal fatigue index (VFI): development and validation. J Voice 29(4):433-440
49. Paolillo NP, Pantaleo G (2015) Development and validation of the voice fatigue handicap questionnaire (VFHQ): clinical, psychometric, and psychosocial facets. J Voice 29(1):91-100
50. M. Hirano (1981) Clinical examination of voice. Springer-Verlag New York
51. Poburka BJ, Patel RR, Bless DM (2017) Voice-vibratory assessment with laryngeal imaging (VALI) form: reliability of rating stroboscopy and high-speed videoendoscopy. J Voice 31(4):513.e1-513.e14
52. Carroll TL, Wu YHE, McRay M, Gherson S (2012) Frame by frame analysis of glottic insufficiency using laryngovideostroboscopy. J Voice 26(2):220-225
53. Desuter G, Dedry M, Schaar B, van Lith-Bijl JT, van Benthem PPG, Sjögren EV (2018) Voice outcome indicators for unilateral vocal fold paralysis surgery: a review of the literature. Eur Arch Otorhinolaryngology 275(2):459-468
54. Hakkesteegt MM, Wieringa MH, Gerritsma EJ, Feenstra L (2006) Reproducibility of the Dutch version of the Voice Handicap Index. Folia Phoniatr Logop 58(2):132-138
55. Van Gogh CDL, Mahieu HF, Kuik DJ, Rinkel RN, Langendijk JA, Verdonck-de Leeuw IM (2007) Voice in early glottic cancer compared to benign voice pathology. Eur Arch Otorhinlaryngology 264(9):1033-1038