

## REVIEW

## Reinke's edema management and voice outcomes

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## Abstract

**Objectives:** Reinke's edema is a chronic disease of the respiratory tract that occurs in adults with a history of chronic smoke exposure. Also known as polypoid corditis, polypoid laryngitis, and polypoid degeneration of the vocal fold, it is strongly associated with smoking, frequently with vocal misuse/abuse, and occasionally with laryngopharyngeal reflux. Reinke's edema remains a cause of chronic dysphonia that is difficult to manage. This review provides perspectives on current and future management of Reinke's edema.

**Results:** Reinke's edema impacts <1% of the population. The excessive mass is seen in polypoid degeneration results in a loss of pitch control and a rough voice. Women are more likely to present for treatment as the characteristic lowering of vocal pitch is more noticeable in women than men. Multiple grading systems have been proposed within the literature. The current standard of care is surgical excision, after smoking cessation. The microflap technique remains the approach of choice for bulky lesions. Surgical management of Reinke's edema has evolved with the introduction of various lasers into otolaryngologic practice; some which can now be used in the office setting. While many management approaches have been described within the literature, there is a little direct comparison<sup>2</sup> and no obvious superior method of Reinke's edema management.

**Conclusion:** To date, the biology of Reinke's edema is not well understood. Additional research is needed further elucidate the role of uncontrolled reflux in the development and recurrence of Reinke's edema.

## KEYWORDS

dysphonia, polypoid corditis, Reinke's edema, smoking

## 1 | INTRODUCTION

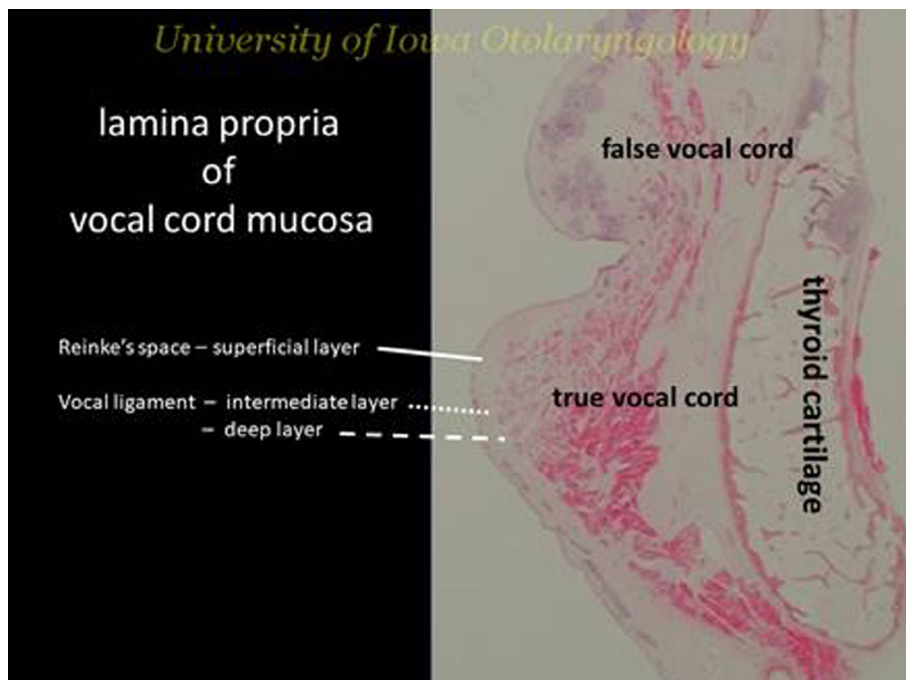
Reinke's edema is a chronic benign inflammatory condition of the larynx involving vascular congestion and swelling of the superficial lamina propria of the vocal fold, Reinke's space.<sup>1</sup> Also known as polypoid corditis, polypoid laryngitis, and polypoid degeneration of the vocal fold, it is strongly associated with smoking, frequently with vocal

misuse/abuse and occasionally with laryngopharyngeal reflux. The late stage of Reinke's edema is the polypoid degeneration of the vocal folds where edema fluid decreases and is replaced by fibrous tissue septa that cause the polypoid appearance of the vocal folds. The excessive mass is seen in polypoid degeneration results in a loss of pitch control and a rough voice. The common pathway by which these lesions affect the voice is disruption of the mucosal vibratory function.<sup>2</sup>

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**FIGURE 1** Cross-sectional anatomy of the human vocal fold. Reinke's space. Hoffman HT (ed) Iowa Head and Neck Protocols "Vocal fold hemorrhage, Vocal cord bleed, Vocal varix, Telangiectasia" <https://medicine.uiowa.edu/iowaprotocols/vocal-fold-hemorrhage-vocal-cord-bleed-vocal-varix-telangiectasia> accessed April 27, 2022



## 1.1 | Demographics

The prevalence of Reinke's edema is less than 1% in the general population.<sup>3</sup> Women appear to be affected by RE more often than men. However, it may appear this way because women are more likely to note the decrease in fundamental frequency as compared to men. Multiple risk factors have been identified, most important of which is cigarette smoking, laryngopharyngeal reflux disease, and phonotrauma. The main risk factor for Reinke's edema and for its recurrence is tobacco use. The clinical manifestation of disease is related to the number of cigarettes smoked daily and the duration of exposure to smoke. Longer durations of exposure to cigarette smoke result in higher degrees of histologic damage.<sup>4</sup> There is a higher prevalence of snoring and obstructive sleep apnea in patients with Reinke's edema as demonstrated by Hamdan et al.<sup>5</sup> Additionally, the patients with Reinke's had higher Epworth Sleepiness Scale scores than those OSA patients who did not have concomitant Reinke's edema.

## 1.2 | Clinical presentation

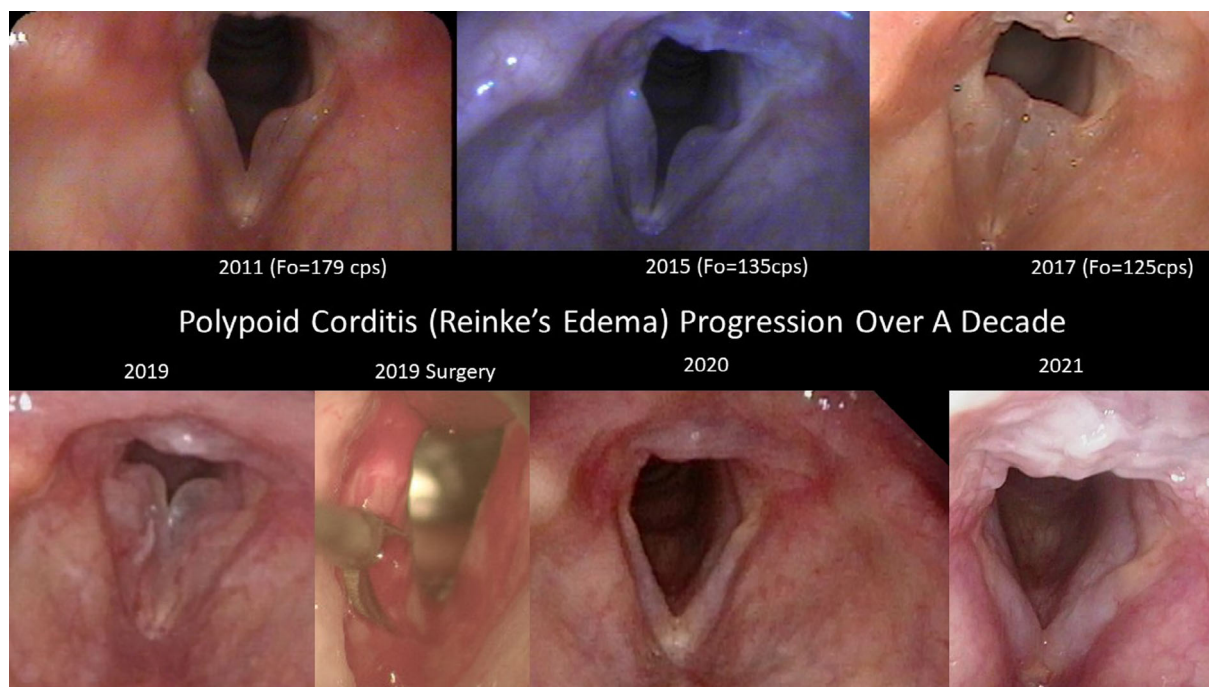
Reinke's space has an average thickness of 0.3 mm. This space contains loosely interwoven collagen and elastic fibers<sup>6</sup> (Figure 1). Reinke's edema can develop unilaterally or bilaterally. Patients with Reinke's edema are plagued by varying degrees of dysphonia. Additionally, some will report dyspnea; however, this is dependent upon the degree of edema and subsequent airway obstruction. It can be intermittent or consistent. Dysphonia is characterized by deepening of the voice, vocal fatigue, decreased vocal range, and loss of high notes. This deepening of the fundamental frequency and poor

durability of voice are typically what lead female patients to seek treatment. Women with Reinke's edema are frequently identified as men when on the phone or speaking without being seen. This has been attributed to the lower  $F_0$  that is characteristic of Reinke's edema patients.<sup>7</sup>

On laryngeal examination, various degrees of balloon-like swelling of the vocal folds are seen (Figure 2). Figure 2 shows a case of a 60-year old-woman. She works as an administrative assistant with high vocal demands. Her past medical history is significant for uncontrolled gastroesophageal reflux and tobacco use with progression of polypoid corditis. While she initially presented with dysphonia in 2011, she was treated surgically in 2019.

On stroboscopy the altered viscoelastic properties of the superficial layer of the lamina propria result in asymmetry, increased mucosal wave propagation and increased amplitude. Radiographic imaging is not required to diagnose Reinke's edema, as the diagnosis is evident on laryngoscopy. However, if imaging is obtained, it is important for the radiologist to be aware of this entity as the soft tissue thickening produced by Reinke's edema can be easily mistaken for tumor infiltration of the vocal folds.

It is important to be aware of the likelihood of Reinke's edema when taking a patient with a significant smoking history to the operating room. Reinke's edema often narrows the glottic aperture. Smaller sized endotracheal tubes may be needed to achieve intubation.<sup>8</sup> Delivery of positive pressure ventilation through a supraglottic device may be impeded by billowing of the edematous folds and resultant glottic obstruction. This can be erroneously attributed to device mispositioning or laryngospasm. Fiberoptic examination through the device can help to delineate the cause.<sup>9</sup> Preexisting Reinke's edema contributes to worsening laryngeal edema in certain circumstances, such as surgery in the prone or Trendelenburg position and excessive



**FIGURE 2** A 60-year-old woman presented with dysphonia in 2011. This figure demonstrates her progression of Reinke's edema as she continued to smoke until surgical resection was performed in 2019. The fundamental frequency of her voice ( $F_0$ ) is included for reference, showing the lowering of her pitch with the worsening of Reinke's edema. Hoffman HT (ed) Iowa Head and Neck Protocols "Polypoid Corditis (Reinke's Edema) Progression Over A Decade" <https://medicine.uiowa.edu/iowaprotocols/polypoid-corditis-reinkes-edema-progression-over-decade> accessed April 27, 2022

fluid administration. Before extubation these patients would benefit from an assessment of the degree of laryngeal edema either visually or with a cuff leak test. Considerations in such patients include extubating over an airway exchange catheter or postponing extubation until edema subsides. Intravenous steroids help decrease inflammatory edema.<sup>8</sup>

### 1.3 | Grading system

Throughout the literature several classification systems for Reinke's edema have been proposed. Yonekawa et al. proposed a system based on morphological features of the vocal fold when visualized under indirect laryngoscopy. They described Type 1 as edema of the superficial aspect of the vocal folds, Type 2 as edema extending to the posterior portion of the vocal folds and Type 3 as massive edema.<sup>10</sup> Tan et al. have proposed a grading system based on degree of airway obstruction. There are 4 grades—Grade 1 in which the lesion involved <25% of the glottic airway, Grade 2 25–50%, Grade 3 50–75%, and Grade 4 > 75% obstruction.<sup>11</sup> Most recently de Vincentiis et al. have proposed a classification based upon the morphological characteristics of the Reinke's edema. They attempt to combine the vocal fold characteristics and the airway obstruction description into one system. "Type 1: RE of one vocal fold, Type 2: RE of both vocal folds, Type 3: RE of one vocal fold with a polypoid lesion, Type 4: RE of both vocal folds with polypoid lesions."<sup>12</sup>

### 1.4 | Pathophysiology

Reinke's edema is an inflammatory disorder characterized by the chronic accumulation of fluid in the superficial layer of the lamina propria. While the primary etiology is prolonged smoke exposure, both vocal abuse and gastroesophageal reflux also contribute to the morphologic changes of the mucosal fold. These include the expansion of the subepithelial space, secondary to transudate, vascular congestion, and venous.<sup>13–15</sup> Chronic irritation from smoking and acid reflux increases capillary permeability, leading to edema and polypoid degeneration of the true vocal folds. This causes the vocal cords to appear swollen and translucent. It is important to note that fluid can accumulate acutely in Reinke's space via different processes than the development of chronic Reinke's edema. Traumatic laryngitis, the most common cause of dysphonia, is caused by an acute accumulation of fluid in Reinke's space. However, polypoid corditis more commonly known as Reinke's edema is mentioned in the literature as synonymous with the concept of chronicity.<sup>16</sup>

The flexible framework which maintains the uniformity of the lamina propria is lost in Reinke's edema. This is caused by the disarrangement of collagen fibers. Sakae et al. examined 20 vocal fold specimens with Reinke's edema. The intertwined network of collagen fibers resembling a wicker-basket that is normally seen in the vocal fold was disarranged in Reinke's edema. In the Reinke's edema samples the fibers were loosely arranged, fragmented and intermixed with varying amounts of myxoid stroma. Moderate and large areas of

disarrangement predominated. The fibers were no longer parallel to the epithelial basement membrane, but had a random distribution scattered throughout Reinke's space. Collagen fiber arrangement in the region underneath the epithelium was better preserved when compared with fibers in the deeper region of the superficial layer of the lamina propria. The disarrangement of elastic fibers in Reinke's edema may cause insufficient tissue resistance and resilience, contributing to the hypermobility observed in Reinke's edema.<sup>17</sup> CD34+ fibroblasts are a major cell component in the stroma of vocal folds in Reinke's edema.<sup>18</sup>

The primarily histopathologic features include epithelial thickening, hyperkeratosis, basement membrane thickening, vessel proliferation, hemorrhage, submucosal edematous lakes, inflammatory infiltrates, and fibrosis.<sup>19</sup> The lining of the edematous lakes consists of compressed fibroblasts. There is a loss of fibronectin, collagen, and elastin from the basement membrane and lamina propria. Making the vocal fold more deformable. Injury to the capillary endothelium with subsequent extravasation of fluid into the potential space is the initial trauma leading to the development of edema. The swelling probably occurs from the increased aerodynamic pressures that drive vocal fold mucosal oscillation in a general environment of glottal mucositis, which is secondary to smoking and reflux. The swelling is typically bilaterally but often asymmetric in volume.<sup>20</sup> Changes in the composition of the vocal fold extracellular matrix such as reduction of collagen fibrils and increase of hyaluronan lead to the clinical changes characteristic of Reinke's edema.<sup>21</sup> The vocal folds of patients with Reinke's edema have much higher concentrations of hyaluronic acid as compared to controls.<sup>22</sup> Histopathologic analysis demonstrates a moderate expression of hepatocyte growth factor in the lamina propria. This growth factor acts as an anti-fibrotic agent in Reinke's space and impacts the fibronectin deposition in the lamina propria. MIB-1 in contrast shows weak expression in the basement membrane of the mucosal epithelium and absence in the deep layer of the lamina propria. MIB-1 is anti-Ki67. Ki67 is a cell proliferation marker, utilized as a proliferation marker in many neoplastic lesions. The absence of MIB-1 in the deep layer of the lamina propria indicates that only the superficial layer is actively involved in the reparatory process with a high regenerative capacity, together with a high deposition of fibronectin. This is necessary for cellular connection reconstruction, after the inflammatory infiltration.<sup>23</sup>

Toohill suggested in 1997 that uncontrolled laryngopharyngeal reflux could be a causative factor in the polypoid degeneration of the vocal folds. The authors go on to assert that this patient population predominately consists of elderly females who do now rely on their voice for their profession but do have a long history of smoking.<sup>24</sup> A progressive increase in the fluid and edema in Reinke's space traverses the entire length of the TVC. This subepithelial compartment is between the mucosa of the TVC and the vocal ligament, which covers the vocalis muscle. The boundaries of Reinke's space are superiorly the vocal fold epithelium, cranially the superior arcuate line, caudally the inferior arcuate line, anteriorly Broyle's ligament, posteriorly the arytenoid and deep the vocal ligament (Figure 3). Hirano first described Reinke's space as composed of amorphous substance that

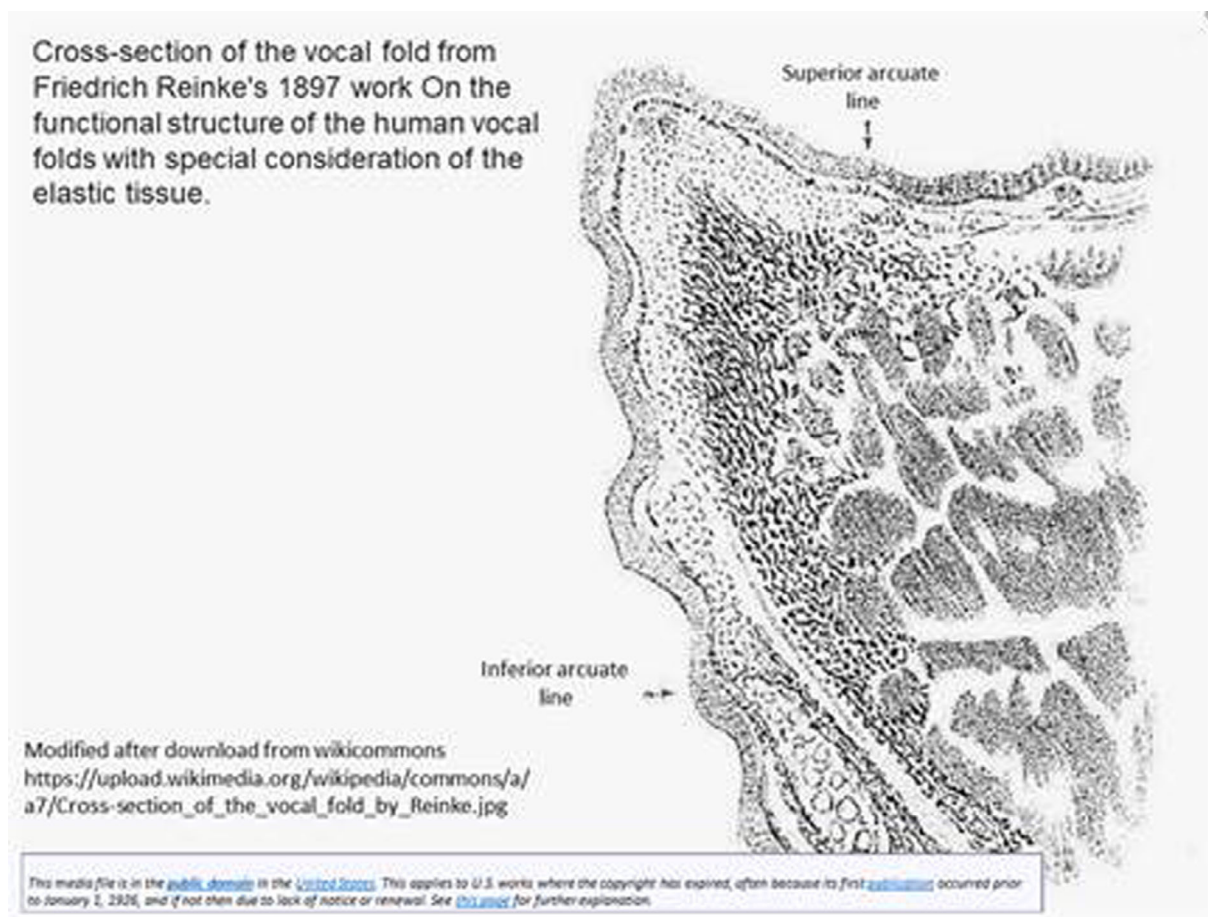
is loose and pliable underlying the epithelium and clearly delineated from the intermediate layer of the lamina propria which defines the medial border of the vocal ligament. Reinke's space is a potential space for the accumulation of material as may occur with vocal fold trauma, vocal fold hemorrhage or polypoid corditis. The superficial lamina propria (Reinke's space) vibrates during phonation, facilitated by the viscoelasticity of its extracellular matrix composed of reticular, collagenous and elastic fibers. The arcuate line is considered the border between the squamous epithelium of the vocal fold and high columnar epithelium on the dorsal and ventral sides.<sup>25</sup> Anti-reflux therapy, smoking cessation, and voice therapy will aid in reducing this edema but phonosurgical removal is usually necessary. It is important to continue the above-mentioned conservative measures for a prolonged period postoperatively to insure a better rehabilitation of voice. In a large study conducted in South Korea, Chung et al. documented LPR in 16 of 18 patients with Reinke's edema.<sup>26</sup> Katsinelos et al. investigated the occurrence of both chronic laryngitis and Reinke's edema. Similar to other studies, the authors found a significant association between GERD, chronic laryngitis, and Reinke's edema.<sup>27</sup> In their 2009 study Chung et al. noted a significantly higher rate of LPR in those patients with Reinke's edema as compared to controls.<sup>26</sup>

## 1.5 | Malignancy risk

Tobacco exposure is a risk factor for both RE and cancer. Given the almost universal prevalence of smoking in patients with Reinke's edema, the coexistence of invasive squamous cell carcinoma or dysplastic changes might be expected in a significant proportion of these patients. To date it has been reported in several populations that the prevalence of coexistent dysplastic or malignant changes is low. No statistical correlation has been identified between RE and the severity of dysplasia noted on surgical specimens at the time of biopsy. The size of the Reinke's edema lesion is not a reflection of premalignancy. The majority of RE lesions, regardless of size, have little to no premalignant potential. More severe dysplasia/carcinoma in situ may be more likely to be found in grade 4 lesions; however, the paucity of severe dysplasia published in RE data precludes any formal inference.<sup>28</sup> Lim et al. indicate in their 2014 retrospective study on 189 patients with Reinke's edema over a 10-year period, 170 had no dysplasia, 16 had mild dysplasia, 2 had moderate dysplasia, and 1 had severe dysplasia. There was no malignancy reported. The epithelium appeared to differentiate to benign Reinke's edema rather than malignancy. There is low risk of malignancy in Reinke's edema.<sup>29</sup> However, Reinke's edema has been reported to cause false-positive fluorodeoxyglucose (FDG) uptake on PET/CT. A laryngoscopic examination and often histopathologic examination is necessary to verify the PET scan findings.<sup>30</sup>

## 1.6 | Surgical management of Reinke's edema

Initial management of Reinke's edema usually includes recommendation to stop smoking and undergo voice therapy.<sup>31-33</sup> When the



**FIGURE 3** Cross sectional anatomy of the human vocal fold showing the arcuate line, borders of Reinke's space. Hoffman HT (ed) Iowa Head and Neck Protocols "Vocal fold hemorrhage, Vocal cord bleed, Vocal varix, Telangiectasia" <https://medicine.uiowa.edu/iowaprotocols/vocal-fold-hemorrhage-vocal-cord-bleed-vocal-varix-telangiectasia> accessed April 27, 2022

improvement in voice is not satisfactory for the patient, surgical intervention should be the treatment of choice.<sup>34</sup> Uncontrolled LPR is associated with impaired re-epithelialization of the vocal folds after surgical procedures for Reinke's edema.<sup>35</sup> The goal of surgical management of Reinke's edema is two-fold. First, to reduce the degenerated excess superficial lamina propria and secondly to preserve the healthy vibratory lamina propria and epithelium. However, it is important to remember that surgical intervention is the first line of treatment when a patient presents with dyspnea, airway compromise, or respiratory distress. Postoperatively, it is important to restore motion of the epithelial layer over the ligament as well as to avoid development of scar. Several therapeutic modalities have been described. Surgical intervention involves making a precise excision of the edematous superficial lamina propria while leaving some gelatinous material to ensure future propagation of the mucosal wave. Surgical intervention may differ based upon different surgical technique and instruments used. After surgical intervention, the inciting stimulus should be reduced whether it is smoking, reflux, or vocal overuse. Postoperative voice therapy is also integral in producing the best possible voice outcome. Surgical intervention for RE can be performed with cold steel technique or with the help of a laser. The mostly

commonly utilized lasers are the carbon dioxide (CO<sub>2</sub>), potassium titanyl phosphate (KTP) laser, and 445 nm wavelength laser (blue laser).<sup>36-38</sup>

### 1.7 | Cold steel technique

First described by Hirano, also called the microflap technique, a vertical incision is made on the superior edge of the vocal fold parallel to the lateral edge. Then the edematous matrix is aspirated. The amount of hyperplastic tissue removed should allow restoration of the normal morphology of the glottis. Tissue removal must proceed from the front to the back without involving the mucosa at the anterior commissure. The excessive epithelium is then excised from the free edge and placed back down. This approach preserves the vibratory edge of the vocal fold as the incision is made far lateral to the medial or phonatory surface. This technique decreases the mass of the vocal folds and widens the glottis, thereby improving the aerodynamic conditions of phonation. It improves the quality of phonatory movements of the vocal folds, as it maintains their layered, functional structure. This in turn leads to improvement in their Voice related quality of life

scores.<sup>39,40</sup> Courey et al and Zeitels et al demonstrated that normal mucosal waves are rarely restored despite the use of Hirano's microflap technique.<sup>20,41</sup> By comparing the postoperative RFS and RSI scores between Reinke's edema patients with LPR who were treated with PPI and those who were not, Kantas et al. showed that LPR influences epithelialization and recurrence of Reinke's edema in the vocal folds after partial or total decortication.<sup>35</sup> Schyberg et al. assessed voice outcomes after cold steel phonosurgery for Reinke's edema and noted that the mean fundamental frequency significantly increased and the jitter decreased significantly both returning to normal ranges. All patients on stroboscopic examination had a reduction in edema.<sup>42</sup>

## 1.8 | Microdebrider

Edema reduction with minimal mucosal damage is the surgical strategy recommended for earlier and optimal return of voice. When using the microdebrider an initial incision is made on the superior surface of the vocal fold using microscissors. An epithelial lateral microflap is raised with an elevator dissector. As the microflap is retracted laterally with an open triangle forceps, the myxoid stroma in the superficial lamina propria is suctioned and excised using a microdebrider with laryngeal blade. This is similar to the traditional cold steel technique described by Hirano but uses a microdebrider rather than a suction.<sup>43</sup> After a sufficient amount of abnormal superficial lamina propria is removed, the excessive mucosa is trimmed and the lateral microflap is redraped. In a cohort of 5 female patients, 6 months after surgical treatment with the microdebrider patients were noted to have a close-to-normal mucosal waves with respect to amplitude and phase symmetry. There was recovery in loudness and pitch in all patients with near normal to normal voice.<sup>31</sup>

In a systematic review of treatment approaches to Reinke's edema 10 articles described 6 different methods of management. These included: microlaryngeal phonosurgery using cold instruments, the microdebrider, combined CO<sub>2</sub> laser and cold instruments, photoangiolytic laser and steroids and hyaluronidase injection. This review concluded that microdebrider approach was superior as substantiated by great improvement of the patients' voice quality and edema grading by the GRBAS scale and the endoscopic picture. The oscillatory knife and the low suction pressure produce a bloodless operative field leading to flawless resection and good voice outcomes.<sup>16</sup> Burduk et al report their experience using the microdebrider as compared to the CO<sub>2</sub> laser for Reinke's edema management. They report significant postsurgical improvement in the GRBAS score in patients treated with the microdebrider in both the first and third months after surgery. The voice parameters: F<sub>0</sub>, jitter, shimmer, and maximum phonation time significantly improved with the microdebrider group as compared to the CO<sub>2</sub> laser group. The results in microdebrider group also revealed close-to-normal mucosal waves in all patients regarding amplitude and phase symmetry.<sup>44</sup> The better voice parameters observed after microdebrider surgery are likely secondary to more effective vibratory function. This is the direct result of lower scarring and damage to the

lamina propria by using low suction and gentler removal of the pathology with an oscillatory knife.<sup>31,43</sup>

## 1.9 | Lasers

Since the early 1970s, the carbon dioxide laser (CO<sub>2</sub>) has become an indispensable instrument in microsurgery of the larynx.<sup>45</sup> It can be efficiently used to resect Reinke's edema. The vessels on the upper surface of the vocal fold are coagulated and the epithelium is incised in a microflap technique. This flap is medialized and the accumulated fluid within Reinke's space is aspirated. With the CO<sub>2</sub> laser, the bleeding is minimal, making the vocal ligament easily identified. The microflap is then put back in place. If after the removal of edema there is excess epithelium, this can be resected with the laser. The redundant mucosa can be safely removed restoring the optimal vocal fold contour. Remacle et al. reported an increase of the median F<sub>0</sub> from 160 to 182.5 Hz after CO<sub>2</sub> laser resection of Reinke's edema. Specifically for the women in their cohort the median F<sub>0</sub> increased from 170 to 195 Hz. A satisfactory recovery of the mucosal wave may take up to 3 to 4 weeks.<sup>34</sup> Dursun et al. employed a combination of CO<sub>2</sub> laser and cold excision in their cohort. They noted no significant scarring on the vocal folds and remarkable improvement in the mucosal wave as judged by videostroboscopy. They noted significant postsurgical improvement of GRBAS scores of all patients. The low preoperative F<sub>0</sub> values were significantly increased after surgery. The parameters of jitter, shimmer, and noise-to-harmonic-ratio were also significantly improved postoperatively. On the basis of perceptual and acoustic analysis of voice, it can be stated that the quality of voice after surgery was remarkably better than before surgery.<sup>45</sup> This is congruous with other reports in the literature.<sup>20,33,34,40,46</sup>

Non-ablative in-office laser management of Reinke's edema was first described using the pulse dye laser, followed by the KTP and more recently by the CO<sub>2</sub> laser. In these methods no immediate size reduction is achieved. The laser is used in a noncontact mode to achieve blanching, or minor disruption of the epithelium. The superior and medial surfaces are treated, staying far away from the ligament, minimizing scarring. At the conclusion of the procedure, the appearance should reveal scattered blanching of the tissue without significant reduction in mass. In the first 1 to 4 weeks after treatment, the voice may worsen as the vocal folds develop stiffness and inflammation. The final extent of Reinke's edema regression and maximal voice outcome should be noted 5 weeks after intervention. This method is particularly useful for those patients with mild to moderate disease burden. In a retrospective case series patients with less severe Reinke's edema were noted to have greater improvement in the Voice Handicap Index scores.<sup>47</sup>

The photoangiolytic laser, KTP and PDL, is effective in improving polypoid degeneration by ablating damaged microvasculature within the SLP, ultimately inducing the regression of nonvascular pathologic tissue.<sup>48,49</sup> Mouadeb and Belafsky assert in their 2007 publication of 117 in office treatments using PDL that the use of PDL for unsedated office laryngeal surgery is effective. They report a statistically

significant mean VHI improvement in their cohort of patients with Reinke's edema. The limited risk of vocal fold scarring with the PDL has reduced the threshold for surgery on Reinke's. They go on to say that the PDL laser is a very effective and minimally invasive method to treat Reinke's edema.<sup>50</sup> Although it is typically recommended that patients quit smoking, it is not a prerequisite for in-office PDL reduction as it is with patients who will undergo microlaryngeal surgery. Pitman et al. reported positive results using the KTP laser in the treatment of Reinke's edema. In their cohort of seven adult women undergoing in-office KTP laser treatment for RE, there was an improvement in maximum phonation time, and VHI score. The fundamental frequency of the treated patients increased. Stroboscopic findings demonstrated an intact mucosal wave. Histologic comparison of the tissue in 3 patients demonstrated changes in vocal fold vascularity but no acute or long-term damage to the overlying epithelium,<sup>47</sup> indicating that KTP is a safe and effective tool for the management of Reinke's edema in the office setting. In a retrospective review of nine patients who underwent KTP laser treatment of Reinke's edema patients, VHI-10 was noted to decrease significantly.<sup>49</sup> The authors concluded that KTP laser can be safely and effectively used to improve voice in RE patients regardless of severity.

The latest addition to the armamentarium of in office lasers is the blue laser. The combination of photoangiolytic and cutting properties in one wavelength at 445 nm, along with the ability of being transmitted through small glass fibers and the portability of the laser, the blue laser appears to be a promising alternative in the office-based laryngeal laser surgery. Its characteristic wavelength of 445 has unique properties which include a high level of absorption in hemoglobin, collagen, and melanin but lower absorption in water compared to other diode lasers.<sup>38</sup>

### 1.10 | Injection of hyaluronidase

In 2018, Woo described the use of hyaluronidase for the treatment of Reinke's edema. Hyaluronidase is a preparation of proteolytic enzyme. The mechanism of action is by enzymatic degradation of hyaluronic acid. In Reinke's edema that is an overexpression of hyaluronic acid in the lamina propria. Surgical intervention is the gold standard of treatment. However, this may not be necessary with the injection of hyaluronidase. In a series of 6 patients with Reinke's edema treated with hyaluronidase there was good improvement of the edematous changes after injection. While not all of the swelling and corditis resolved, none of the patients had to undergo additional surgery.<sup>51</sup>

### 1.11 | Intralesional steroid injection

Intralesional steroid injection targets the chronic inflammatory process involved in Reinke's edema. It has been reported in retrospective and prospective case series. For mild cases of Reinke's edema complete remission was demonstrated in 33% of cases while partial remission was noted in 60%. Some authors advocate repeat injections in

patients with recurrence.<sup>52</sup> Based upon the hypothesis that Reinke's edema is related to an abnormal inflammatory process, local steroid injections would be expected to disrupt the pathophysiology of these lesions. However, the recurrence rate is relatively high, indicating the limited efficacy of intralesional steroid injections when used alone for Reinke's edema. Steroid injection has also been done in conjunction with cold steel excision of Reinke's edema. Since excessive fibrosis and scarring of the vocal folds after surgery may hamper mucosal vibration, the use of steroid injections is reasonable to reduce fibrosis of the vocal folds. It does not appear to impair wound healing.<sup>53</sup>

It is important to note that abnormalities caused by smoking in Reinke's edema in women are not fully reversible with surgery and smoking cessation. This is likely secondary to the presence of structural alterations in fibroblasts caused by the toxicity of cigarette components. This leads to the uncontrolled production of fibrinous matrix in the lamina propria thereby preventing complete vocal recovery.<sup>54</sup> While many management approaches have been described within the literature, there is very little direct comparison and no obvious superior method of Reinke's edema management. Microendoscopy of Reinke's space, a novel approach, has made it possible to inject materials into Reinke's space with minimal disruption of vocal fold mucosa.<sup>55,56</sup> The injection of stem cells, an approach trialed in the porcine model, may prove to have some utility in the management of Reinke's edema after removal of excess superficial lamina propria.<sup>57</sup>

## 2 | CONCLUSIONS

Reinke's edema is a chronic diffuse edema of the superficial lamina propria. It is caused by chronic exposure to tobacco smoke. Uncontrolled gastroesophageal reflux and voice overuse may also contribute to the development and worsening of Reinke's edema. The most common complaint of a patient with Reinke's edema is dysphonia, or lowering of the voice. However, the most concerning symptom is dyspnea. The primary treatment is surgical intervention while smoking cessation and voice therapy play an adjunctive role. Little research exists comparing the various modalities of surgical intervention. The primary goal is to reduce the edematous matrix of the vocal folds without inducing scar formation. This can be done via cold steel or using a laser. Currently, Reinke's edema is managed by surgical excision primarily, both in the operating room and in the office setting. Tools include the microdebrider, and photoangiolytic lasers like the KTP laser. The advent of the flexible laser system and good topical anesthesia techniques have allowed for office-based procedures to replace OR procedures in mild to moderate cases of Reinke's edema. This is an advantage for both the patient and the surgeon, as it has been shown to decrease procedural time and costs, minimize risks of anesthesia, and allow patients to take less time off work. Patient selection for in-office procedures is dependent upon a variety of factors, including the extent of disease, patient tolerance, and surgeon experience. In conclusion, Reinke's edema is a manageable condition. Smoking cessation is central to reducing recurrence. Voice is shown to improve after smoking cessation and surgical management of

Reinke's edema. Additional research on the ideal management approach is necessary and may lead to the development of novel approaches.

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None.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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## REFERENCES

- Tavaluc R, Tan-Geller M. Reinke's edema. *Otolaryngol Clin North Am*. 2019;52(4):627-635.
- Noordzij JP, Woo P. Glottal area waveform analysis of benign vocal fold lesions before and after surgery. *Ann Otol Rhinol Laryngol*. 2000; 109(5):441-446.
- Hamdan AL, Ghanem A. Un-sedated office-based application of blue laser in vocal fold lesions. *J Voice*. Published online May 21,2021; S0892-1997(21)00126-0.
- Marcotullio D, Magliulo G, Pezone T. Reinke's edema and risk factors: clinical and histopathologic aspects. *Am J Otolaryngol*. 2002;23(2):81-84.
- Hamdan AL, Khalifee E, Abi Akl PR, Ghanem A, El Hage A. Pathogenic role of Reinke's edema in snoring and obstructive sleep apnea. *J Voice*. 2020;34(3):456-459.
- Branski RC, Saltman B, Sulica L, et al. Cigarette smoke and reactive oxygen species metabolism: implications for the pathophysiology of Reinke's edema. *Laryngoscope*. 2009;119(10):2014-2018.
- Pereira AM, Dassie-Leite AP, Pereira EC, Cavichio JB, Rosa MO, Fugmann EA. Auditory perception of lay judges about gender identification of women with Reinke's edema. *Codas*. 2018;30(4):e20170046.
- Sreedharan R, Chhabada S, Khanna S. Reinke's edema: implications for airway management. *Anesthesiology*. 2018;129(4):810.
- Cortegiani A, Rusotto V, Raineri SM, Giarratano A. Should Reinke edema be considered a contributing factor to post-extubation failure? *Crit Care*. 2015;19:430.
- Yonekawa H. A clinical study of Reinke's edema. *Auris Nasus Larynx*. 1988;15(1):57-78.
- Tan M, Bryson PC, Pitts C, Woo P, Benninger MS. Clinical grading of Reinke's edema. *Laryngoscope*. 2017;127(10):2310-2313.
- de Vincentiis M, Ralli M, Cialente F, et al. Reinke's edema: a proposal for a classification based on morphological characteristics. *Eur Arch Otorhinolaryngol*. 2020;277(8):2279-2283.
- Marcotullio D, Magliulo G, Pietrunti S, Suriano M. Exudative laryngeal diseases of Reinke's space: a clinicohistopathological framing. *J Otolaryngol*. 2002;31(6):376-380.
- Byeon H. The association between lifetime cigarette smoking and dysphonia in the Korean general population: findings from a national survey. *PeerJ*. 2015;3:e912.
- Lechien JR, Saussez S, Nacci A, et al. Association between laryngopharyngeal reflux and benign vocal folds lesions: a systematic review. *Laryngoscope*. 2019;129(9):E329-E341.
- Khodeir MS, Hassan SM, El Shoubary AM, Saad MNA. Surgical and nonsurgical lines of treatment of Reinke's edema: a systematic literature review. *J Voice*. 2021;35(3):502 e501-502 e511.
- Sakae FA, Imamura R, Sennes LU, Mauad T, Saldiva PH, Tsuji DH. Disarrangement of collagen fibers in Reinke's edema. *Laryngoscope*. 2008;118(8):1500-1503.
- Diaz-Flores L, Gutierrez R, del Pino GM, Alvarez-Arguelles H, Diaz-Flores L Jr, Lopez-Campos D. CD34-positive fibroblasts in Reinke's edema. *Laryngoscope*. 2014;124(3):E73-E80.
- Goswami S, Patra TK. A clinico-pathological study of Reinke's oedema. *Indian J Otolaryngol Head Neck Surg*. 2003;55(3):160-165.
- Zeitels SM, Casiano RR, Gardner GM, et al. Management of common voice problems: committee report. *Otolaryngol Head Neck Surg*. 2002; 126(4):333-348.
- Gugatschka M, Darnhofer B, Grossmann T, et al. Proteomic analysis of vocal fold fibroblasts exposed to cigarette smoke extract: exploring the pathophysiology of Reinke's edema. *Mol Cell Proteomics*. 2019; 18(8):1511-1525.
- Lins CVM, Maciel Martins JR, Kobayashi EY, et al. Hyaluronic acid concentration in female vocal folds with Reinke's edema. *Otolaryngol Head Neck Surg*. 2021;166:337-342.
- Artico M, Bronzetti E, Ionta B, et al. Reinke's edema: investigations on the role of MIB-1 and hepatocyte growth factor. *Eur J Histochem*. 2010;54(3):e30.
- Toohill RJ, Kuhn JC. Role of refluxed acid in pathogenesis of laryngeal disorders. *Am J Med*. 1997;103(5A):100S-106S.
- Kutta H, Steven P, Paulsen F. Anatomical definition of the subglottic region. *Cells Tissues Organs*. 2006;184(3-4):205-214.
- Chung JH, Tae K, Lee YS, et al. The significance of laryngopharyngeal reflux in benign vocal mucosal lesions. *Otolaryngol Head Neck Surg*. 2009;141(3):369-373.
- Katsinelos P, Kountouras J, Chatzimavroudis G, et al. Should inspection of the laryngopharyngeal area be part of routine upper gastrointestinal endoscopy? A prospective study. *Dig Liver Dis*. 2009;41(4): 283-288.
- Tavaluc R, Herman H, Lin J, Tan M. Does Reinke's edema grade determine premalignant potential? *Ann Otol Rhinol Laryngol*. 2018;127(11): 812-816.
- Lim S, Sau P, Cooper L, McPhaden A, Mackenzie K. The incidence of premalignant and malignant disease in Reinke's edema. *Otolaryngol Head Neck Surg*. 2014;150(3):434-436.
- Erdogan O, Ismi O, Arpacı RB, Vayısoglu Y, Ozcan C. False-positive laryngeal FDG uptake during PET/CT imaging: Reinke's edema. *Turk Arch Otorhinolaryngol*. 2018;56(2):114-116.
- Sant'Anna GD, Mauri M. Use of the microdebrider for Reinke's edema surgery. *Laryngoscope*. 2000;110(12):2114-2116.
- Hojtslet PE, Moesgaard-Nielsen V, Karlsmose M. Smoking cessation in chronic Reinke's oedema. *J Laryngol Otol*. 1990;104(8):626-628.
- Lumpkin SM, Bennett S, Bishop SG. Postsurgical follow-up study of patients with severe polypoid degeneration. *Laryngoscope*. 1990; 100(4):399-402.
- Remacle M, Lawson G, Watelet JB. Carbon dioxide laser microsurgery of benign vocal fold lesions: indications, techniques, and results in 251 patients. *Ann Otol Rhinol Laryngol*. 1999;108(2):156-164.
- Kantas I, Balatsouras DG, Kamargianis N, Katotomichelakis M, Riga M, Danielidis V. The influence of laryngopharyngeal reflux in the healing of laryngeal trauma. *Eur Arch Otorhinolaryngol*. 2009;266(2): 253-259.
- Hu HC, Lin SY, Hung YT, Chang SY. Feasibility and associated limitations of office-based laryngeal surgery using carbon dioxide lasers. *JAMA Otolaryngol Head Neck Surg*. 2017;143(5):485-491.
- Sridharan S, Achlatis S, Ruiz R, et al. Patient-based outcomes of in-office KTP ablation of vocal fold polyps. *Laryngoscope*. 2014;124(5): 1176-1179.
- Hess MM, Fleischer S, Ernstberger M. New 445 nm blue laser for laryngeal surgery combines photoangiolytic and cutting properties. *Eur Arch Otorhinolaryngol*. 2018;275(6):1557-1567.
- Ura-Sabat K, Morawska J, Domka W, Gamrot-Wrzol M, Scierski W, Niebudek-Bogusz E. The assessment of phonatory and ventilatory functions in patients after microsurgery for Reinke's edema. *Adv Clin Exp Med*. 2020;29(7):865-871.



40. Hirano S, Yamashita M, Kitamura M, Takagita S. Photocoagulation of microvascular and hemorrhagic lesions of the vocal fold with the KTP laser. *Ann Otol Rhinol Laryngol*. 2006;115(4):253-259.
41. Courey MS, Gardner GM, Stone RE, Ossoff RH. Endoscopic vocal fold microflap: a three-year experience. *Ann Otol Rhinol Laryngol*. 1995; 104(4 Pt 1):267-273.
42. Schyberg YM, Bork KH, Sorensen MK, Rasmussen N. "Cold-steel" phonosurgery of Reinke edema evaluated by the multidimensional voice program. *J Voice*. 2018;32(2):244-248.
43. Honda K, Haji T, Maruyama H. Functional results of Reinke's edema surgery using a microdebrider. *Ann Otol Rhinol Laryngol*. 2010;119(1): 32-36.
44. Burduk PK, Wierzychowska M, Orzechowska M, Kazmierczak W, Pawlak-Osinska K. Assessment of voice quality after carbon dioxide laser and microdebrider surgery for Reinke edema. *J Voice*. 2015; 29(2):256-259.
45. Dursun G, Ozgursoy OB, Kemal O, Coruh I. One-year follow-up results of combined use of CO<sub>2</sub> laser and cold instrumentation for Reinke's edema surgery in professional voice users. *Eur Arch Otorhinolaryngol*. 2007;264(9):1027-1032.
46. Moesgaard Nielsen V, Hojslet PE, Palvio D. Reinke's oedema: a pre-malignant condition? *J Laryngol Otol*. 1986;100(10):1159-1162.
47. Pitman MJ, Lebowitz-Cooper A, Iacob C, Tan M. Effect of the 532 nm pulsed KTP laser in the treatment of Reinke's edema. *Laryngoscope*. 2012;122(12):2786-2792.
48. Koszewski IJ, Hoffman MR, Young WG, Lai YT, Dailey SH. Office-based photoangiolytic laser treatment of Reinke's edema: safety and voice outcomes. *Otolaryngol Head Neck Surg*. 2015;152(6):1075-1081.
49. Young VN, Mallur PS, Wong AW, et al. Analysis of potassium titanyl phosphate laser settings and voice outcomes in the treatment of Reinke's edema. *Ann Otol Rhinol Laryngol*. 2015;124(3):216-220.
50. Mouadeb DA, Belafsky PC. In-office laryngeal surgery with the 585 nm pulsed dye laser (PDL). *Otolaryngol Head Neck Surg*. 2007; 137(3):477-481.
51. Woo P. Hyaluronidase injection in the vocal folds for vocal hemorrhage, Reinke edema, and hyaluronic acid overinjection: a novel application in the larynx. *J Voice*. 2018;32(4):492-498.
52. Tateya I, Omori K, Kojima H, Hirano S, Kaneko K, Ito J. Steroid injection for Reinke's edema using fiberoptic laryngeal surgery. *Acta Otolaryngol*. 2003;123(3):417-420.
53. Jang JY, Kim DY, Lee GY, et al. Voice outcomes after laryngeal micro-surgery with adjunctive steroid injection for Reinke edema. *Clin Exp Otorhinolaryngol*. 2021;14(3):362-364.
54. Martins RH, do Amaral HA, Tavares EL, Martins MG, Goncalves TM, Dias NH. Voice disorders: etiology and diagnosis. *J Voice*. 2016;30(6): 761 e761-761 e769.
55. Hoffman HT, Bock JM, Karnell LH, Ahlrichs-Hanson J. Microendoscopy of Reinke's space. *Ann Otol Rhinol Laryngol*. 2008;117(7):510-514. discussion 515-516.
56. Bartlett RS, Hoffman HT, Dailey SH, et al. Restructuring the vocal fold lamina propria with endoscopic microdissection. *Laryngoscope*. 2013; 123(11):2780-2786.
57. Woo JH, King SN, Hoffman H, et al. MERS versus standard surgical approaches for porcine vocal fold scarring with adipose stem cell constructs. *Otolaryngol Head Neck Surg*. 2016;155(4):612-623.

#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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