

表2 術後聴取能 (術後2年以上経過例)

症例	1	2	3	4	5	6	7	8	9	10	11	12
奇形	L	L	L	M	M	M	M	M	M	H	A	A
手術 年齢	13Y 10M	2Y 4M	4Y 0M	1Y 6M	4Y 0M	3Y 1M	11Y 10M	2Y 2M	3Y 10M	3Y 1M	5Y 11M	3Y 1M
術前 聴力	S.O	100dB	S.O	S.O	S.O	110dB	S.O	100dB	S.O	S.O	90dB	S.O
装用 期間	3Y 10M	4Y 0M	4Y 6M	5Y 3M	6Y 1M	2Y 1M	7Y 0M	2Y 3M	2Y 9M	9Y 8M	5Y 0M	3Y 4M
NRT	+	+	+	+	-	-	+	+	-	-	-	-
語音 弁別	母音	母音	母音	母音	母音	母音	母音	分節	母音	母音	不良	不良
	100%	100%	100%	100%	100%	100%	100%	100%	60%	100%		
	子音	子音	子音	子音	子音	子音	子音	子音	子音	子音		
	100%	80%	85%	100%	62%	70%	62%		不良	65%		
	分節		分節	分節	分節	分節	分節			分節		
	100%		100%	100%	60%	100%				80%		
装用 閾値	30dB	35dB	38dB	25dB	33dB	30dB	38dB	30dB	40dB	40dB	33dB	判定 困難

L: 前庭水管拡大症、M: Mondini奇形、H: 蝸牛低形成、A: 半規管無形成
手術年齢・装用期間は年(Y)月(M)で表記、S.O: スケールアウト

形があっても乳突蜂巣を含めた中耳形態が正常であれば、経乳突洞・後鼓室開放による通常のアプローチで手術可能であった。一方で、乳突蜂巣發育不良を伴う中耳奇形を合併した内耳奇形では経外耳道アプローチが必要となり、顔面神経走行異常に遭遇する可能性もあるため、手術施行に際しては細心の注意が必要と思われる。またMondini奇形など外側半規管低形成を伴う症例で外側半規管隆起の高さを指標に後鼓室開放を行った場合には、顔面神経走行異常がなくても術者の予想より外側に顔面神経が出現する可能性にも注意が必要である。

内耳奇形例のなかで、蝸牛がincomplete partitionを示し、前庭水管拡大とlarge vestibuleを特徴とする、いわゆる古典的Mondini奇形や前庭水管拡大症(単独)では良好な術後成績が多く報告されているが^{4),5)}、今回の検討でも中耳奇形を合併したMondini奇形1例を除き同様の結果であった。一方で、半規管無形成例、蝸牛低形成例、common cavity型例では術後成績は劣ることが多いとされる^{4),6),7)}。我々の経験した蝸牛低形成例は比較的良好な成績であったが、半規管無形成例は2例ともに語音聴取は不良であり、内耳奇形タイプによる術後聴取能の差異が認められた。人工内耳術後成績には様々な要因が関与しているが、残存ラセン神経節細胞数の観点から見ると、人工内耳に必要最小限な残存ラセン神経節細胞数は正常の1割もしくは5000個程度と考えられてい

る⁸⁾。高度難聴児の蝸牛ラセン神経節細胞数は正常と比べ平均46%で、通常軽度の内耳奇形では人工内耳に必要最小限な蝸牛ラセン神経節細胞数が残存していることが多いが⁹⁾、時に極端に神経節細胞数が減少している場合もあるため⁹⁾、CT画像で描出される骨迷路の形態異常の程度のみで残存神経節細胞数を予想することは難しい。我々も聴取能不良なMondini奇形例を経験したが、同じ内耳奇形タイプでも術後聴取能に極端な差が生じる可能性を念頭に置く必要があると思われた。

内耳奇形例の人工内耳手術では蝸牛開窓時の過剰な脳脊髄液の漏出(いわゆるCSF gusher)の可能性があり、内耳奇形タイプ別では、内耳道奇形、common cavity型、蝸牛低形成、蝸牛水管拡大、前庭水管拡大症候群などで生じやすく、特にcommon cavity型ではリスクが高いとされている^{5),10)}。Gusherが生じた場合、蝸牛開窓部の嚴重なパッキングのみで対応できる例も多く報告されているが、中耳腔、耳管の充填を要する場合もある¹⁰⁾。さらに中耳腔の徹底した充填を行っても脳脊髄液漏が停止しない場合には持続腰椎ドレナージを行うが、施行に伴う合併症を考慮すると可能な限り避けるべきであるとの意見もある¹⁰⁾。今回4例(22%)で脳脊髄液の漏出が見られ、内耳道奇形とMondini奇形の各1例では多量の漏出であったが、幸い蝸牛開窓部のパッキングで対応できた。

NRTを用いた聴神経複合活動電位測定は大多数例で安定して反応が得られ、特に術中測定では100%の症例で計測可能であったとする報告も見られる^{11)~13)}。内耳奇形例であっても前庭水管拡大症例では聴神経複合活動電位が得られるとの報告があるが¹⁴⁾、一方でMondini奇形例においては反応が得られなかったり¹²⁾、反応が不安定であった¹⁴⁾との報告がある。今回の検討でも前庭水管拡大症では全例測定可能であったが、Mondini奇形では3分の1、半規管無形成・蝸牛低形成例ではいずれも術中聴神経複合活動電位が測定できなかった。また術後2年以上経過した時点での聴取能不良例は全例で術中NRT反応が不良であり、聴覚予後不良を予測する指標のひとつになると思われた。しかし術中反応が無くても術後聴取能良好例もあり、少なくとも術中反応が得られた場合には聴覚予後良好といえる。

人工内耳のハード、ソフト両面での進歩は著しく、今後高性能機器の出現とさらに精緻なコード化法の開発が期待されるため、内耳奇形を伴う小児高度難聴例に対して人工内耳を選択する機会が今後増加することが予想される。今回の検討では、内耳奇形の中で頻度の高いMondini奇形の大部分や前庭水管拡大症では良好な術後聴取成績を示したが半規管無形成例など術後聴取能不良な場合があること、また術中CSF漏出のリスクはあるものの非内耳奇形例とはほぼ同様の手技で手術可能な内耳奇形例が多いが、中耳奇形合併例や内耳道奇形例では手術困難となる場合もあることが示され、術前に人工内耳装用効果不十分となる場合を想定した説明が必要と思われる。特に術中NRT検査で反応がない場合には約半数で術後聴取能不良であり慎重な経過観察が必要であろう。

ま と め

- 1) 内耳奇形を伴う小児人工内耳手術例18例を報告したが、これは小児人工内耳例全体の約17%に相当した。
- 2) 内耳奇形例の手術はCSF漏出の可能性にも配慮する必要があるものの非内耳奇形例と同様の経乳突洞アプローチ・後鼓室開放で78%が施行可能であり、また88%の症例で全活動電極が挿入可能であった。しかし、中耳奇形を合併する症例では経外耳道アプローチが必要で、顔面神経走行異常を伴う場合もあった。
- 3) 術後聴取能は内耳奇形タイプによる差がみられ、前庭水管拡大症、Mondini奇形ではおおむね良好だが、半規管無形成例では不良であった。また術後聴取不良例では術中NRT検査で反応が得られなかった。

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Regeneration of Aged Vocal Fold: First Human Case Treated With Fibroblast Growth Factor

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Background/Objectives: Aged vocal folds are characterized by atrophy of the mucosa, which causes dysphonia and is difficult to treat. We have revealed a therapeutic potential of basic fibroblast growth factor (bFGF) for tissue regeneration of the aged vocal fold. We report here the first human case that has been treated with bFGF.

Study Design: Institutional review board approved clinical human trial.

Methods: A 63-year-old man with atrophied vocal folds was treated by local injection of 10 μ g of bFGF into the left vocal fold under topical anesthesia. The effects of the injection were examined after 1 to 3 months by videostroboscopy, acoustic and aerodynamic measurements.

Results: The atrophy of the vocal fold was improved at 1 week after the injection and glottic gap disappeared. Aerodynamic and acoustic parameters also showed remarkable improvement. These positive effects were maintained up to 3 months.

Conclusion: The first case with aged vocal folds treated with bFGF administration is presented. The results are encouraging, suggesting therapeutic effects of bFGF for atrophied vocal folds in human.

Key Words: Aged vocal fold, basic fibroblast growth factor, regeneration.

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INTRODUCTION

Voice changes with age. It tends to become weak, harsh and breathy, especially in men.¹ This voice change is caused by the atrophy of the vocal fold which induces bowing, glottal insufficiency, and reduction of the mucosal

traveling wave.^{2,3} The atrophy occurs because of histological alterations of the lamina propria of the vocal fold, including excessive collagen deposition with formation of thick bundles, reduction of elastin and hyaluronic acid (HA).^{4–7} It is required to address these histological changes to restore the aged vocal fold.

Fibroblasts in the lamina propria are the main provider of extracellular matrix (ECM). It has been revealed that fibroblasts decrease in number with age, and intracellular presence of golgi apparatus and rough endoplasmic reticulum also decrease, which suggests reduction of activity to synthesize ECM.^{8,9} Therefore, it may be important to activate fibroblasts and control their function of ECM production to produce sufficient HA and suppress excessive collagen synthesis.

Basic fibroblast growth factor (bFGF) is a stimulant of growth of fibroblasts, and also induces modification of ECM production from the cells. In our previous in vitro study using aged rats has indicated that bFGF stimulates cell growth of fibroblasts in the aged vocal folds, and also induces a significant increase of HA production from those cells and suppresses production of collagen type I.¹⁰ These effects seemed to be favorable for restoration of aged vocal fold lamina propria to younger state.

The effects of local administration of bFGF into aged vocal folds were also examined in our subsequent in vivo study using aged rats.¹¹ The results showed a recovery of HA content in the lamina propria of aged vocal folds in the bFGF treated group, which suggested a therapeutic potential of bFGF to restore an appropriate viscoelasticity of the vocal folds.

We then set up a protocol of use of bFGF for human cases with atrophied vocal folds caused by aging, which was approved by the institutional review board of Kyoto University. We report here the first human case treated by bFGF.

MATERIALS AND METHODS

Preparation of bFGF

Product of bFGF solution usable for human (Fibrast) was developed by Kaken Pharmaceutical (Tokyo, Japan) using artificial recombination of genes of human bFGF. Fibrast was

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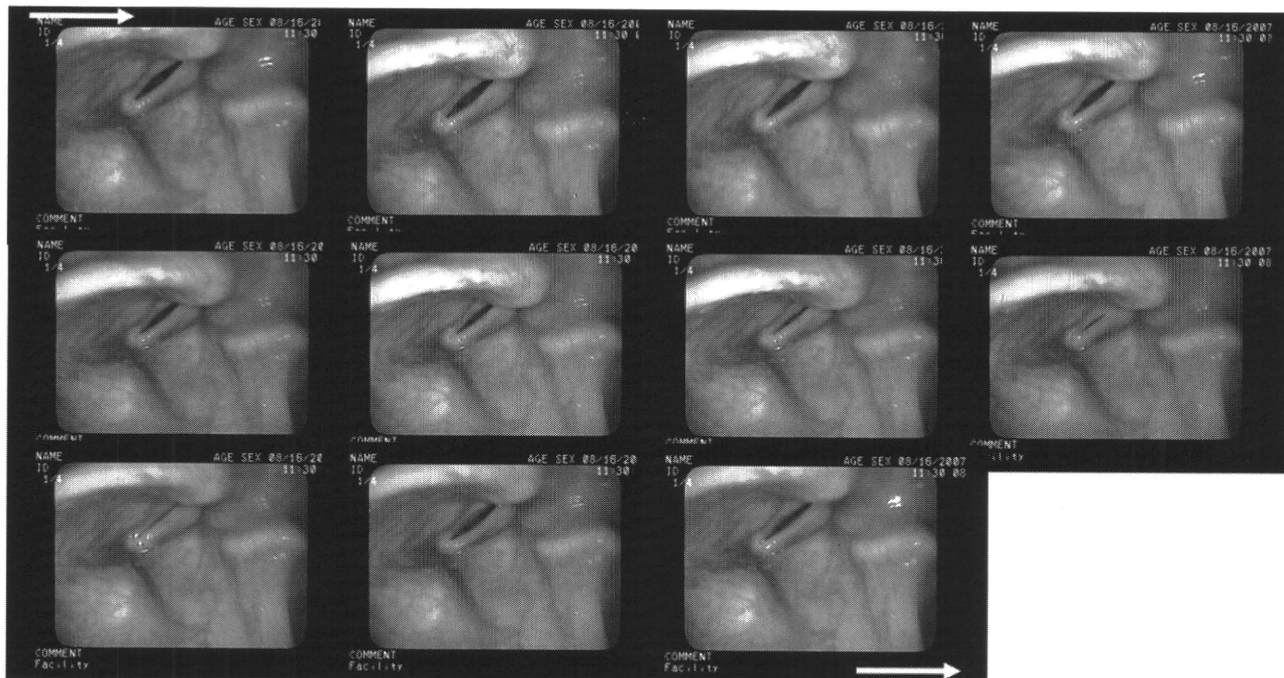


Fig. 1. Pretreatment videostroboscopic findings. Mucosal wave was reduced and glottic closure was incomplete.

approved for the treatment of skin ulcer in Japan and other limited countries, but not in the United States. No major safety issue has been reported so far. The only concern is that bFGF stimulates tumor growth if the patient has neoplasm on the applied site. Therefore, it is prohibited to use bFGF on the site of cancer.

Protocol

Unilateral transoral injection of bFGF (Fibrast, Kaken, Tokyo) is planned for patients, older than 50 years old, with vocal fold atrophy which causes hoarseness. Exclusion criteria include patients with organic or neurogenic voice disorders, a history of malignant tumors, hepatic diseases, kidney dysfunction, or other severe systemic disorders. Ten microgram of bFGF in 0.5 mL saline is prepared for local injection into the vocal fold. The dose was determined after one time dose of 10 to 20 μ g used for skin. bFGF is injected into the superficial layer of the lamina propria under topical anesthesia using a curved injection needle. The injection is performed on one side because of safety issue. It is

always required to minimize any unexpected adverse effects in a clinical trial.

The effects of the injection are assessed after 1 to 3 months by videostroboscopy, acoustic and aerodynamic examinations.

Patient

A 63-year-old man patient with aged vocal folds was recruited for the current trial. He had complained of a hoarse, breathy voice. Stroboscopic examination showed bilateral vocal fold atrophy with glottic insufficiency and reduction of mucosal wave amplitude (Fig. 1).

Ten microgram of bFGF in 0.5 mL saline was transorally injected into the left vocal fold under videolaryngoscopic monitoring after thorough topical anesthesia by 4% lidocaine spray (Fig. 2). The injection needle was placed at lateral portion of the vocal fold, and the bFGF solution was gradually infiltrated into the whole lamina propria.

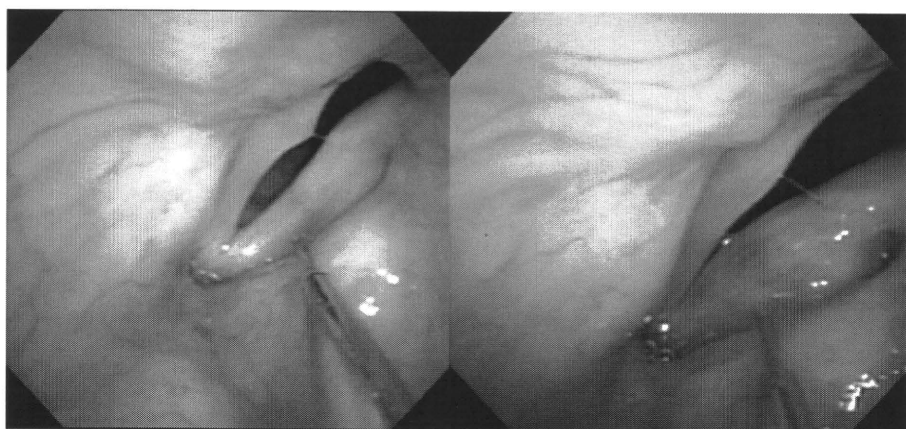


Fig. 2. Injection of bFGF solution under topical anesthesia. Left, injection needle was placed at lateral portion of the vocal fold. Right, Solution was injected inside the lamina propria of the fold.

Assessment

Stroboscopic examinations were performed using Digital Video Stroboscopy System Model 9295 (KayPentax, Lincoln Park, NJ) at 1 week, 1 month, and 3 months after injection to assess

mucosal wave and glottic closure. The amplitude of vibration and glottal gap were examined using image analysis software (Scion Image beta3b, Frederick, MA). The distance (d1) from midline of the glottis to the free edge of the vocal fold was measured at

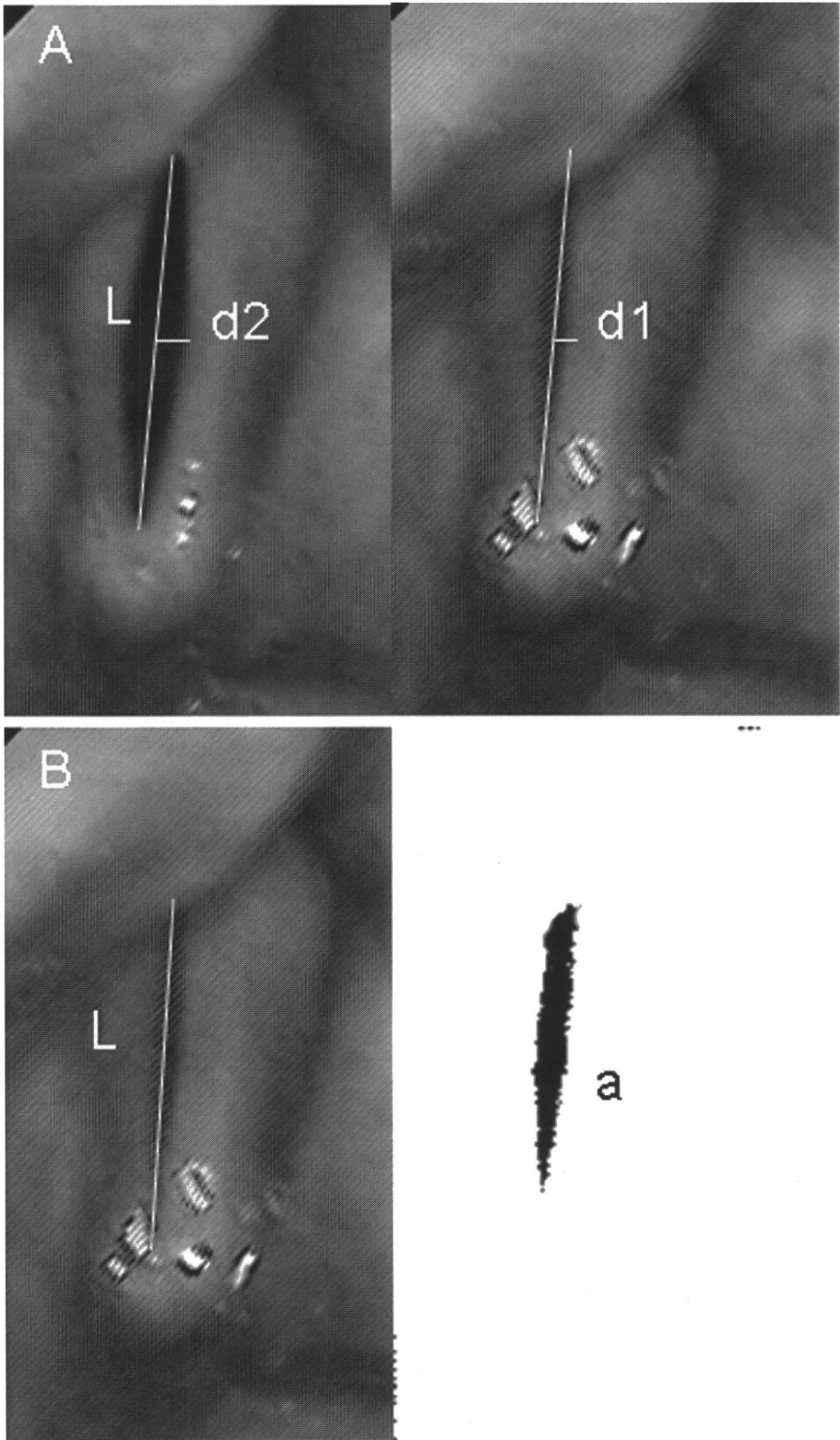


Fig. 3. Measurement of the amplitude of vibration and glottic gap. (A) Normalized mucosal wave amplitude (NMWA) = $(d2 - d1)/L$. (B) Normalized glottic gap (NGG) = a/L^2 . (a: glottic area).

anteroposterior middle portion of the vocal fold at closed phase, and then the same distance (d2) was measured at maximum open phase (Fig. 3A). Mucosal wave amplitude was defined by subtracting d1 from d2, and normalized by dividing them by the length (L) from the anterior commissure to the vocal process: normalized mucosal wave amplitude = (d2 - d1)/L. This measurement was done on the left vocal fold (injected side). Glottal gap was examined on the images at closed phase. Glottal area (a) was measured and then normalized by dividing it by L² (Fig. 3B): normalized glottal gap = a/L².

Aerodynamic and acoustic measures were also completed at the same time points. Aerodynamic examinations included maximum phonation time and mean flow rate. Acoustic analyses evaluated amplitude perturbation quotient, pitch perturbation quotient, and noise-to-harmonic ratio.

RESULTS

Laryngoscopic examination found complete absorption of the injected solution in the vocal fold on the next day. Videostroboscopic examination at 1 week after the injection revealed an improvement of mucosal wave with complete glottic closure, and these positive effects were maintained up to 3 months (Fig. 4). Mucosal wave amplitude (normalized mucosal wave amplitude) and glottic closure (normalized glottal gap) also showed improvements from 1 week through 3 months after the administration of bFGF (Fig. 5).

The voice became stronger with less hoarseness. Maximum phonation time and mean flow rate improved at 1 week to 3 months. Acoustic parameters also showed improvements during the period from 1 week to 3 months (Fig. 6).

DISCUSSION

Vocal fold atrophy is characterized with alteration of histology of the lamina propria of the vocal fold mucosa. The superficial lamina propria is the most important portion for mucosal vibration, and is required to have an ideal viscoelasticity. With age, however, histological studies have revealed thinning of superficial lamina propria. Sato et al.^{5,6} reported an increase of collagen, especially in men, forming thick bundles with high density, accompanied with reduction of elastin. A representative case indicated a massive collagen deposition in the lamina propria, showing no layer structure in the vocal fold mucosa. Excessive collagen deposition is thought to increase tissue strength,¹² which is not a favorable event for vibratory properties.

HA is one of the glycosaminoglycans distributed in the lamina propria. Several studies have indicated that HA is the key ECM molecule that maintains an optimal viscoelasticity of the vocal fold mucosa.^{13,14} However,

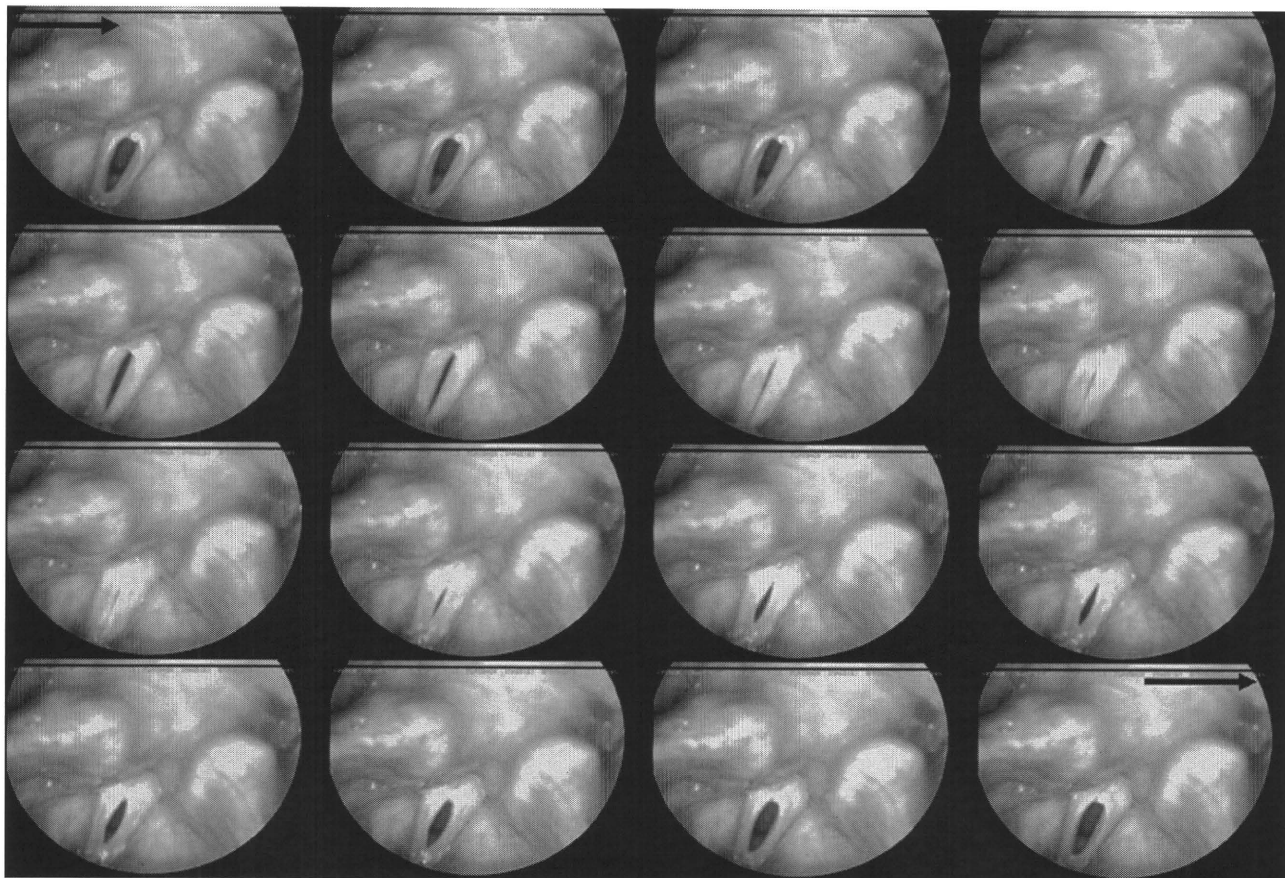


Fig. 4. Videostroboscopic findings at 3 months after bFGF injection. Mucosal wave improved with complete glottic closure.

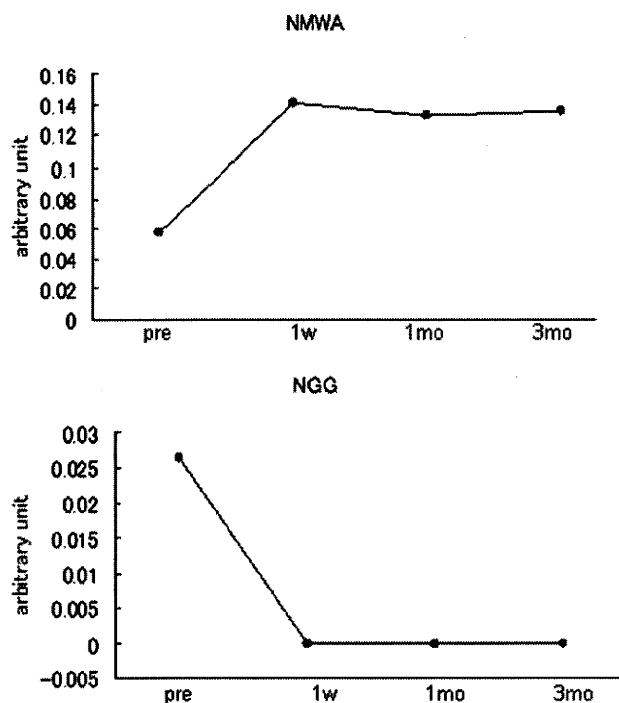


Fig. 5. Normalized mucosal wave amplitude (NMWA) and normalized glottic gap (NGG). Both values showed remarkable improvement after 1 week through 3 months after bFGF administration.

Butler et al.⁷ reported a trend of decrease of HA in the whole lamina propria in human with age.

Above mentioned histological changes are attributed mainly to dysfunction of fibroblasts in the vocal fold with age. Sato et al.⁹ demonstrated a decrease of number of the cells, decreases of intracellular organelle responsible for protein synthesis, and decreases of production of collagen or elastin from the cells, by histological examinations on aged human vocal folds. The macula flava is regarded as a "bank" of fibroblasts which is located at the anterior and posterior ends of the vocal ligament. These cells present with stellate shape and a high potential of ECM production. With age, however, Hirano et al.⁸ showed drastic

histological changes of the cells including changes of shape, poor development of intracellular organelle, increases of glycogen particles and lipofusion granules, suggesting a decrease in activities of protein production. Ding and Gray¹⁵ examined gene expression of ECM in aged rat vocal fold tissues, and found decrease of gene expression of collagen type I, V, and proteinase, which suggested slow-down collagen turnover.

Based on the previously reported histological alterations of aged vocal folds, we have hypothesized that it should be essential and useful to increase HA deposition and decrease collagen to improve the tissue properties of aged vocal folds. We have also acclaimed that such regeneration of vocal fold atrophy requires tissue engineering strategy. Growth factor therapy is one of the most important elements in tissue engineering. Growth factors affect various cells and their function, and in that sense it is important to use them at appropriate places with appropriate dosage, timing, and route.

We have paid extensive attention on bFGF for the treatment of vocal fold atrophy. bFGF stimulates proliferation and migration of fibroblast and keratinocyte,¹⁶ and thus has been used for reepithelialization of intractable skin ulcer. Hom et al.¹⁷ indicated that exogenous bFGF also worked well for an improvement of wound healing of postirradiated skin in a pig study. As a clinical use in otolaryngology, Hakuba et al.¹⁸ reported that topical administration of bFGF prompted regeneration of tympanic membrane in patients with a large perforation of the ear drum.

The effects of bFGF on ECM synthesis have also been well-described. Hong and Trackman¹⁹ reported that bFGF reduced mRNA expression of collagen type I in gingival fibroblasts, while bFGF was reported to stimulate HA synthesis from skin fibroblasts.²⁰ We have also found that bFGF consistently stimulates ingrowths of fibroblasts of aged rat vocal folds, and that bFGF stimulates HA production and suppressed collagen type I production from the aged rat fibroblasts.¹⁰ Based on these results, we were motivated to use bFGF for human patients with vocal fold atrophy caused by aging.

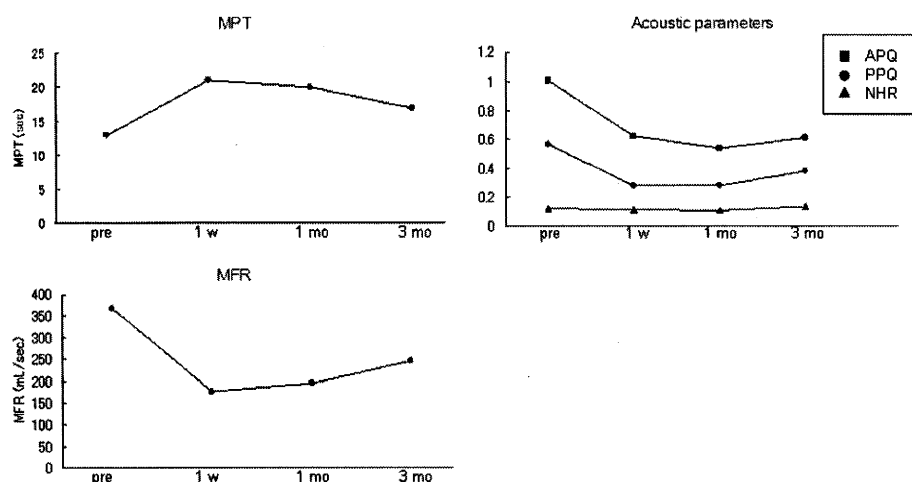


Fig. 6. Aerodynamic and acoustic measurements. MPT, MFR, PPQ, and APQ were improved at 1 week through 3 months after bFGF administration. MPT, maximum phonation time; MFR, mean flow rate; APQ, amplitude perturbation quotient; PPQ, pitch perturbation quotient; NHR, noise to harmonic ratio.

The present case study showed an improvement of tissue property of the aged human vocal fold after injection of bFGF in terms of mucosal vibration, glottic closure, aerodynamic and acoustic parameters. Such effects were already observed at 1 week after the injection. Because the injection material was solution, its volume inside the vocal fold disappeared on the next day, which means there were no effects of augmentation. Therefore biological activity of bFGF was thought to be so strong and rapid to improve the tissue properties of the vocal fold within a week, although it was impossible to confirm actual histological changes in the human study.

The present results have indicated that a single injection of bFGF has an ability to restore and maintain better mucosal vibration of aged vocal folds at least for 3 months, which seems to be quite useful for clinical treatment of human subjects. Growth factor therapy is considered as a "trigger" to jump start biological mechanisms,²¹ which may be the reason why only a single injection of bFGF solution made such drastic effects as seen in the present study. Further studies are necessary to clarify how long the effects last and how consistently it works for different patients. It is at least suggested that the application of bFGF may be useful for regeneration of human aged vocal folds.

CONCLUSION

We report preliminary data of a human clinical trial of bFGF administration for an aged vocal fold. During a short-period observation, sufficient regenerative effects on the tissue properties of the treated vocal fold were noted without any adverse effect or toxicity. It is necessary to carry out further study with more cases and long-term follow up to confirm the regenerative effects of bFGF. It is at least suggested that local administration of bFGF may become a useful tool for the treatment of vocal fold atrophy.

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Replacement of the Left Main Bronchus With a Tissue-Engineered Prosthesis in a Canine Model

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Background. Stenosis of the left main bronchus caused by inflammatory diseases and neoplasms is a serious clinical problem because it can cause obstructive pneumonia and may require pneumonectomy. As an alternative to various treatments currently available, including balloon dilatation, stenting, and bronchoplasty, we propose the use of a prosthesis developed based on the concept of in situ tissue engineering for replacement of the left main bronchus.

Methods. The main frame of the tissue-engineered prosthesis is a polypropylene mesh tube, 12 to 15 mm in inner diameter and 30 mm in length, with reinforcing rings. Collagen extracted from porcine skin is conjugated to this frame. A consecutive series of 8 beagle dogs underwent replacement of the left main bronchus with this tissue-engineered prosthesis.

Results. All dogs survived the postoperative period with no morbidity except 1, which required intravenous

administration of antibiotic for a week for pneumonia and recovered. Three dogs were euthanized for examination at 3 and 4 months after bronchus replacement, and the other five were monitored for more than 1 year. In two dogs, histologic examination revealed that the luminal surface was completely covered with ciliated columnar epithelium or nonciliated squamous epithelium. Exposure of the polypropylene mesh to various degrees was observed in 6 dogs, but the prosthesis remained stable and no adverse effects such as infection, sputum retention, or dehiscence were observed.

Conclusions. These long-term results suggest that our tissue-engineered prosthesis is applicable for replacement of the left main bronchus.

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Various therapeutic approaches for bronchial stenosis and obstruction have been reported, including bronchoscopic dilatation, laser ablation, airway stenting, and surgical bronchoplasty [1–3]. The objective of the present study was to test a possible alternative for the treatment of bronchial stenosis and obstruction. We have been developing a porous type of airway prosthesis conjugated with a collagen layer based on the concept of in situ tissue engineering. The intent of in situ tissue engineering is to create a local environment with a prepared scaffold suitable for tissue or organ restoration [4]. We have applied a collagen layer as a three-dimensional scaffold, which provides an appropriate environment into which surrounding host cells can migrate and proliferate, and applied it for regeneration of the trachea [5–8], esophagus [9, 10], stomach [11, 12], intestine [13], and peripheral nerves [14–16]. Collagen is a major component of the extracellular matrix and is known to promote cellular proliferation and tissue healing.

With this type of prosthesis, we have previously reported replacement of the intrathoracic trachea [5–7] and

carinal part of the trachea [8] in animal experiments and the cervical trachea in humans [17, 18]. On the basis of these experiences, we designed a new prosthesis and adopted it for experimental replacement of the left main bronchus in dogs.

Material and Methods

Bronchial Prosthesis

The collagen-conjugated bronchial prosthesis (20 mm long with an internal diameter of 12 to 15 mm) was made by a method similar to that described in our previous report concerning tracheal and carinal reconstruction [5]. The prosthesis consists of a fine polypropylene mesh cylinder with a pore size of 260 μ m (Marlex mesh, CR Bard Inc, Billerica, MA), reinforced with 5 rings of polypropylene monofilament string (1 mm in diameter) wrapped around it. These rings were attached to the cylinder by thermal melt bonding to maintain the proper cylindrical form. This mesh cylindrical frame was exposed to a corona discharge at 9 kV for 5 minutes to make its surface hydrophilic.

The prosthesis was placed into a mold. A 2% collagen solution (supplied by Nippon Meat Packers Inc, Osaka, Japan) was poured into the mold, followed by freeze-drying, to form a collagen layer 5 mm thick around the

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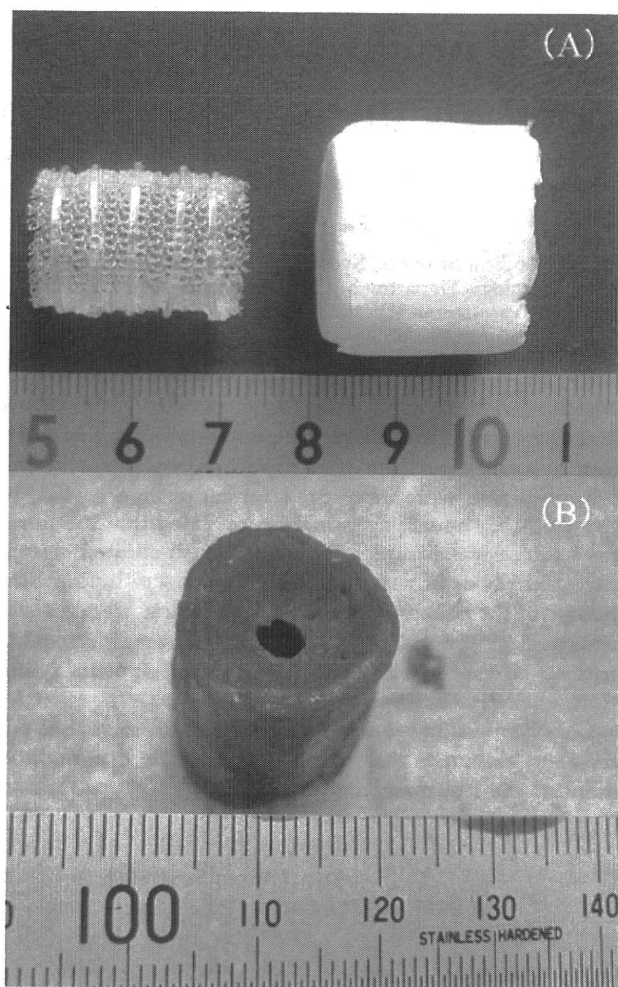


Fig 1. (A) The bulk structure of the prosthesis consists of a mesh cylinder reinforced with 5 rings of polypropylene string (left) and a covering of conjugated collagen (right). (B) This outer view shows the outer prosthesis conjugated with a collagen layer after it has been soaked with blood, just before replacement.

frame. In this process, the collagen became an amorphous layer with a pore size of 100 to 500 μm . The prosthesis was heated at 140°C under vacuum for a single or double 24-hour session of dehydrothermal treatment to induce moderate cross-linkage in the collagen molecules. Finally, the prosthesis was sterilized with ethylene oxide gas and stored dry until use. Figure 1A shows the polypropylene frame, and Figure 1B shows the collagen-conjugated prosthesis, which appears swollen after being soaked in blood.

Animal Experiment

Eight adult beagle dogs, weighing 8 kg to 15 kg, were anesthetized by the intramuscular administration of ketamine hydrochloride (15 mg/kg) and xylazine (7 mg/kg) and then intubated with an endotracheal tube. Respiration was maintained by a mechanical ventilator with halothane and nitrous oxide gas. A left thoracotomy was made through the 4th or 5th intercostal space according

to the physique of each dog. The left main bronchus was exposed from the spur of the left upper bronchus to the carinal edge through the pulmonary aorta window. After the main bronchus had been transected at the spur of the left upper bronchus, the distal end was anastomosed with interrupted 3-0 Vicryl suture (Ethicon Inc, Somerville, NJ) to the prosthesis (Fig 2), which had been previously soaked with blood.

A 10-mm segment of the left main bronchus was resected and the carinal stump was anastomosed to the proximal end of the prosthesis. Both ends of the prosthesis were intended to be anastomosed in a telescopic manner, the bronchial end lying inside the prosthesis. A pedicled pericardial fat pad was fixed to the surrounding structure to cover the prosthesis.

The dogs were appropriately hydrated with extracellular fluid, and hydrocortisone (125 mg) was administered during the operation. Ampicillin was given intravenously at a dose of 1 g on the day of the operation and at 0.5 g daily for 3 days thereafter. Hydrocortisone (125 mg) was administered intravenously for 3 days after the procedure. All the animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources, Na-

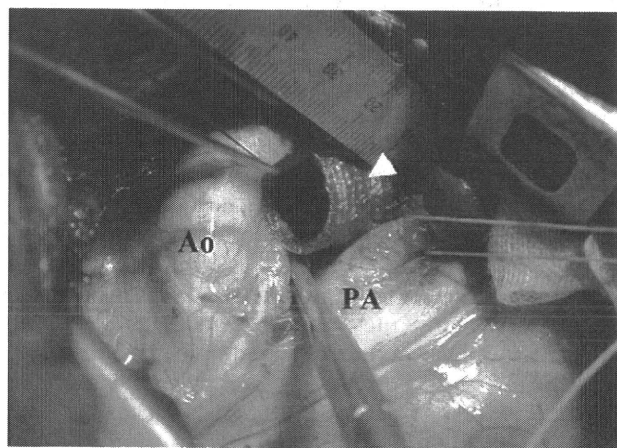
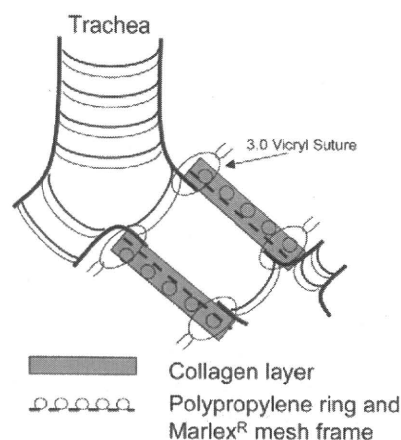
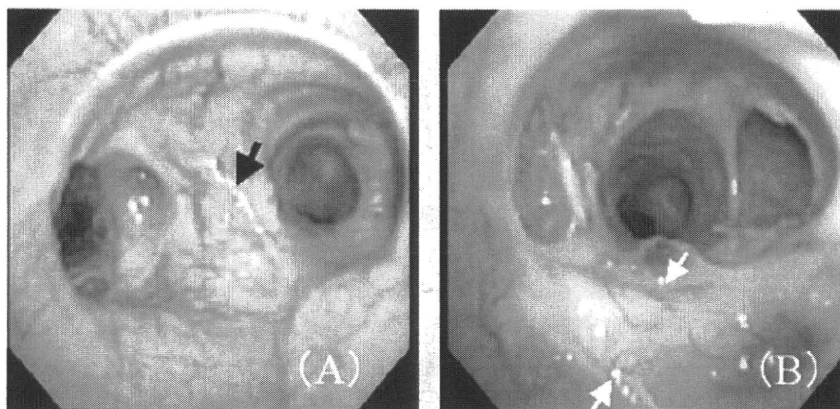


Fig 2. (Top) This drawing shows the schematics of the bronchial reconstruction. (Bottom) This photograph was taken during bronchial replacement with the artificial prosthesis (arrowhead). (Ao = aorta; PA = pulmonary artery.)

Fig 3. (A) Bronchoscopic views of dog 8 taken 18 months after tracheal replacement. Neither stenosis nor granulation is evident at the site of anastomosis. Black arrow shows the carina. The prosthesis was fully covered with regenerated tissue. (B) White arrows show the regenerated portion of the bronchus.



tional Research Councils, National Academy Press, revised 1996.)

Bronchoscopic Observation

Bronchoscopic observation was done periodically after induction of general anesthesia by an intramuscular injection of ketamine hydrochloride and xylazine hydrochloride. The luminal surface was observed with a bronchofiberscope (Model BF1T20, Olympus Optical Company, Ltd, Tokyo, Japan) to evaluate the coverage by host tissue and complications such as stenosis and dislocation of the prosthesis (Fig 3).

Evaluation of the Prosthesis

The replaced portion was examined bronchoscopically and macroscopically (Fig 4) after necropsy. Mesh exposure exceeding one-third of the circumference was defined as "exposed," and less than one-third as "spot exposed." Stenosis was defined as a reduction of more than one-third of the tracheal lumen cross-sectional area. Euthanasia was performed by intravenous injection of ketamine hydrochloride at a dose of 100 mg/kg, followed by necropsy.

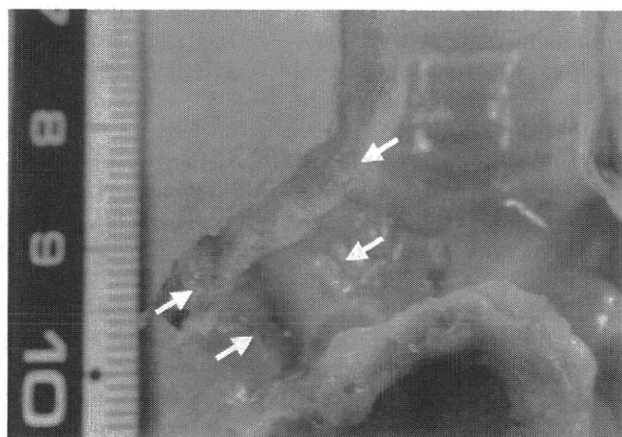


Fig 4. Macroscopic view shows of the luminal surface of the prosthesis of dog 8 at 18 months after replacement. Arrows show the regenerated part. The luminal surface is covered with apparently normal mucosa, which is continuous with the native bronchus and appears whitish.

Histologic Examination

Immediately after macroscopic evaluation, specimens were placed in 10% formaldehyde solution, followed by paraffin embedding. Sections 5 μ m thick were stained with hematoxylin and eosin for light microscopy. Another part of each fresh specimen was fixed with 2% glutaraldehyde and critical-point-dried by Au-Pd sputtering for scanning electron microscopic examination.

Results

The outcome of the experiments is reported in Table 1. All the dogs survived postoperative period without measurable morbidity, but severe pneumonia developed in 1 dog. Bronchoscopic and radiologic findings showed that this pneumonia was caused by postoperative atelectasis. This dog (No. 1 Table 1) recovered after the intravenous administration of antibiotic for a week and showed no dehiscence of anastomosis, or infection to the prosthesis during postoperative period.

Table 1. Results of Replacement of the Left Main Bronchus

Dog	Prosthesis Inner Diameter, mm	Dehydrothermal Treatment Time, hours	Stenosis	Mesh Exposure	Remarks
1	12	48	(-)	Spot	Sacrificed, 4 mon
2	12	48	(+)	(+)	Sacrificed, 3 mon
3	13	48	(+)	Spot	Sacrificed, 18 mon
4	15	48	(-)	(+)	Sacrificed, 4 mon
5	15	48	(-)	(+)	Sacrificed, 18 mon
6	15	24	(-)	(-)	Sacrificed, 18 mon
7	15	24	(-)	(-)	Sacrificed, 18 mon
8	15	24	(-)	(+)	Alive after 18 mon

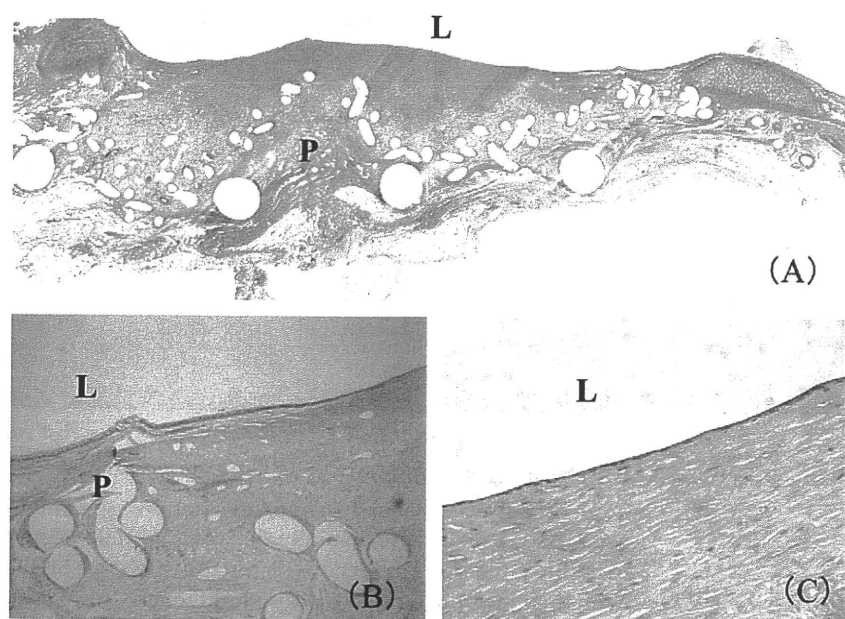


Fig 5. Microscopic examination of a longitudinal section of the regenerated tissue 18 months after replacement (hematoxylin and eosin staining). (A) Regenerated neomucosa with epithelial lining is observed on the prosthesis. (B) Ciliated epithelial cells have grown over the prosthesis showing continuity with the native bronchial epithelia, whereas (C) the center of the prosthesis is covered with a monolayer of squamous epithelium. (L = bronchial lumen, P = polypropylene mesh.) (Original magnification: $\times 10$ for A, $\times 40$ for B, $\times 100$ for C.)

Bronchoscopic and Macroscopic Examination

Stenosis and excessive granulation were observed in dogs 2 and 3. One possible reason for the stenosis might have been mismatching of the prosthesis size in these 2 dogs, the prosthesis diameters being 12 and 13 mm, respectively, which were considered too small for the purpose. No stenosis or excessive granulation developed in the other 5 dogs, whose left main bronchi were replaced with a 15-mm-diameter prosthesis. Thus, the stenosis might have been caused by the small size of the prosthesis.

The evaluation for mesh exposure showed 4 dogs were classified as "exposed," 2 as "spot exposed," and 2 as fully covered. Dogs 2 and 3, which developed excessive granulation and stenosis, also showed concomitant mesh exposure.

Because mesh exposure was prominent in the first 4 dogs in this series, we reduced the dehydrothermal treatment time to 24 hours, with the expectation that this would enhance cell immigration to the prosthesis wall in the last 3 dogs. Complete epithelization was achieved in 2 dogs of this group, but the epithelization remained partial in 1 dog.

The host tissue incorporated into the framework of the prosthesis, and neither erosion nor nonfavorable interaction was observed between the framework and the adjacent vessels. No complications such as hemoptysis or intrathoracic hemorrhage were observed.

Histologic Findings

Ciliated columnar epithelium was microscopically observed near the anastomosis, but the proportion of squamous epithelium became larger than that of ciliated columnar epithelium with increasing distance; near the center of the prosthesis, only squamous epithelium was recognized (Fig 5, Fig 6). No immigration of inflammatory cells under the regenerated epithelium was evident,

indicating that the prosthesis was well incorporated without an excessive foreign body reaction, which may lead to formation of granulation tissue and stenosis.

Comment

Reconstruction of the airway with an artificial prosthesis has been studied for decades. However, the degree of success has been limited because of problems such as local infection, stenosis, or rupture of the adjacent vessels [19-21]. The risk of such fatal complications currently precludes the clinical use of artificial prostheses in this situation.

Most recently, tissue-engineering techniques have been applied to regenerate a biologic prosthesis for implantation. Using *ex vivo* tissue engineering techniques, Kojima and colleagues [22] successfully created a tissue-engineered trachea with regenerated cartilage from bone marrow cells. However, the transplantation of such *ex vivo* tissue-engineered tissues has been associated with poor functional outcome [23, 24], and so their application is still problematic.

Another biologic approach for creation of prostheses has been reported by Martinod and colleagues [25]. They applied allogenic aorta for tracheal replacement, and the transplant was proven to be functional after removal of the inner stent [25, 26]. It is noteworthy that the allotransplant was replaced by a completely regenerated trachea provided with cartilage rings derived from the recipient. There is a similarity between their approach and ours, because the basic idea of *in situ* tissue engineering is to produce an environment suitable for host tissue regeneration at the required site.

The aortic graft played the role of a biologic incubator to allow host cells to migrate into it and form the regenerated trachea. One dissimilarity was that we used a polypropylene permanent framework as a substitute

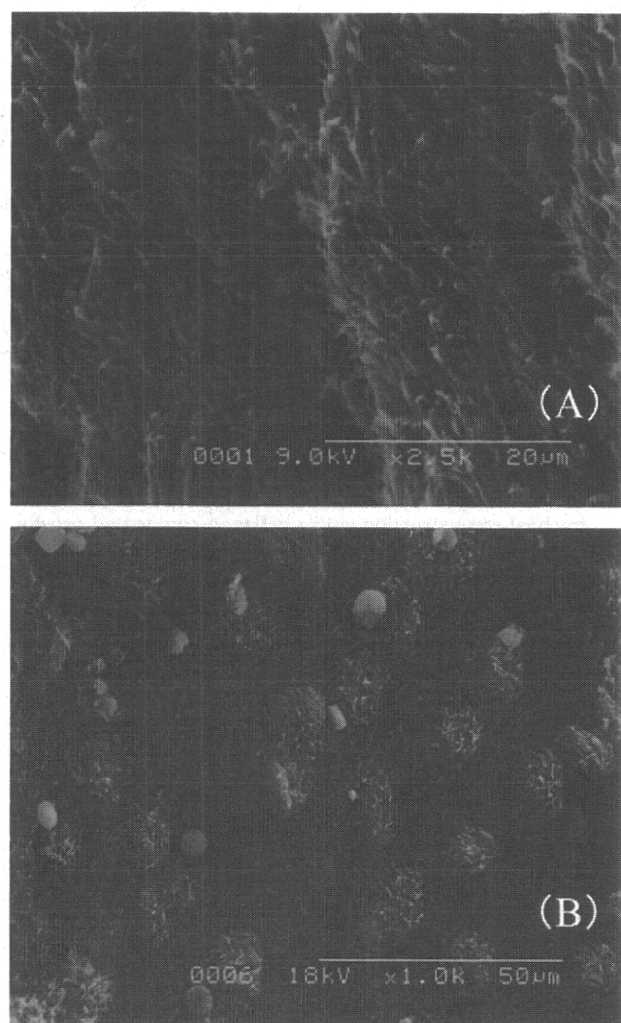


Fig 6. Scanning electron microscopy findings of the prosthesis 18 months after replacement. (A) The proximal portion of the anastomosis is covered with ciliated epithelial cells ($\times 2500$; bar, $20\ \mu\text{m}$), whereas (B) fewer such cells are observed in the middle of the prosthesis ($\times 1000$; bar, $50\ \mu\text{m}$).

for cartilage, whereas they applied an internal stent temporarily. Wurts and colleagues [27] have reported clinical application of this type of approach, and we await their long-term results, which may indicate whether cartilage would be generated in adult humans.

The requirements for an ideal prosthesis are (1) adequate durability that can be maintained long enough to restore the functional airway, (2) high biocompatibility, enabling incorporation into the host tissue, and (3) relatively low cost. We have been investigating a tissue-engineered collagen-conjugated prosthesis that potentially meets these requirements. Okumura and colleagues [5] designed a tracheal prosthesis consisting of a rigid polypropylene frame and a collagen monolayer. Animal experiments showed that this type of prosthesis has high biocompatibility with host tissue and overcomes serious major complications such as anastomotic leakage or postanastomotic stenosis. [7] With regard to mechan-

ical properties, this type of tissue-engineered tracheal prosthesis has appropriate mechanical properties similar to those of the native trachea [28], and its feasibility has been proven by observation for more than 5 years in a canine tracheal replacement model [29]. For the cervical trachea, Omori and colleagues [17, 18; unpublished data] have applied this tissue-engineered tracheal prosthesis for 8 patients to date, with a maximum follow-up period of 4 years.

In terms of biocompatibility, we have developed a prosthesis conjugated with a thick collagen layer after a trial with a collagen monolayer type. Using this type of prosthesis, Teramachi and colleagues [6, 7] have achieved intrathoracic tracheal replacement, and Sekine and colleagues [8] have reported that a Y-shaped prosthesis for carinal reconstruction in a canine model showed good incorporation into the host tissue [6]. We consider that the collagen layer, which has a three-dimensional structure and provides an appropriate extracellular matrix in which migrating cells can proliferate, potentially enhances tissue regeneration.

As for affordability, this type of prosthesis is suitable for commercial production in various sizes and lengths at a low cost compared with biologic transplants and is free from any risk of donor infection. We used ethylene oxide gas for sterilization, because gamma-ray irradiation may have a degradative effect on collagen fibers. Gorham and colleagues [30] reported that neither method of sterilization of collagen-based wound repair materials produced any cytotoxic effect, although gamma-ray sterilization, which is more convenient, did lead to accelerated absorption.

On the basis of our previous experiences, we designed a prosthesis for replacement of smaller portions of the airway and applied it for repair of left main bronchial defects in a canine model. The aim of the present study was to clarify whether our previously developed tissue-engineered prosthesis would be applicable for smaller airway defects and to determine the optimum conditions for its use.

Severe stenosis developed in 2 of 3 dogs in which the left main bronchus was replaced with a 12-mm-diameter prosthesis. In contrast, no stenosis developed in the 5 dogs in which the bronchus was replaced with a 15-mm prosthesis. These results show that the inner diameter of the prosthesis should be 15 mm for replacement of the canine left main bronchus, which has a caliber of 10 to 12 mm, as measured at the site during the operation.

For the preparation of the collagen solution and the conditions for cross-linkage of the collagen molecules, we started with 1% collagen solution and 24 hours of dehydrothermal treatment. However, in the 2 dogs that received this type of prosthesis, the disruption of the prosthesis wall caused tension pneumothorax that proved to be too fragile for sealing the peripheral airway without an inner lining. These initial 2 dogs that were fitted with the 1% collagen prosthesis were therefore eliminated from the study. A prosthesis made with 2% collagen and cross-linked for 48 hours was applied in consecutive experiments, and the wall of this prosthesis

proved sufficiently durable to withstand the airway pressure. However, mesh exposure was prominent with this type of prosthesis, and epithelization of the lumen was poor compared with our previous study, in which 90% of dogs showed no mesh exposure.

Unlike our previous procedures for replacement of the intrathoracic trachea and carina [6, 8], we did not insert a silicone tube inside the prosthesis for extraction 8 weeks after implantation. This silicone tube had played a role in protecting the collagen layer from early degradation before tissue formation. However, because the canine left bronchus was considered too small for application of a silicone tube, we intended to try a simpler procedure. To improve epithelization, we reduced the dehydrothermal treatment time. Dehydrothermal treatment for 48 hours gives the collagen layer mechanical strength but may denature the collagen and thus decrease its favorable characteristics. Although we have not performed a sufficient number of trials to obtain precise data, it appears that collagen loses its ability to promote cell proliferation after 48 hours of dehydrothermal treatment because of excessive cross-linkage between the collagen molecules. Prostheses coated with 2% collagen that had been exposed to dehydrothermal treatment for 24 hours were transplanted with the expectation that this reduction in dehydrothermal treatment time would improve tissue regeneration. Two of the three dogs showed complete epithelization and no mesh exposure, and none showed dehiscence, disruption of the prosthesis wall, or stenosis. We therefore concluded that coating with 2% collagen solution and 24 hours of dehydrothermal treatment are the optimum conditions for preparation of the prosthesis.

In this canine model using the left main bronchus, the time for tissue regeneration was estimated to be 3 to 4 weeks by bronchoscopic observation. In patients where the cervical trachea was reconstructed, tissue regeneration was considered to take rather longer; Omori and colleagues [18] reported that this period ranged from 2 to 11 months in patients undergoing cervical tracheal replacement. Because no infection or dehiscence before complete epithelization occurred in these patients, mesh exposure might not be a fatal problem. However, to accomplish better epithelization, we are now investigating an improved prosthesis in which the luminal surface is lined with biodegradable polymer. In this new trial, we are observing better epithelization, with 90% of candidates accomplishing complete epithelization, although the observation period is not yet long enough.

We designed a new prosthesis for peripheral airway reconstruction. In a canine left main bronchus replacement model, this collagen-conjugated polypropylene prosthesis showed sufficient mechanical strength to support the airway without causing stenosis, and good biocompatibility. Although further assessment is essential before clinical application, our designed prosthesis may be a promising alternative for the treatment of left main bronchial stenosis and obstruction.

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Notice From the American Board of Thoracic Surgery Regarding Trainees and Candidates for Certification Who Are Called to Military Service Related to the War on Terrorism

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Richard H. Feins, MD
Chair
The American Board of Thoracic Surgery

Endoscopic KTP Laser Photocoagulation Therapy for Pharyngolaryngeal Venous Malformations in Adults

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Objectives: Venous malformations are benign lesions with thin, fragile mucosa overlying a vascular stroma. Vascular anomalies often manifest as subglottic lesions in infants, but venous malformations in adults are rare in the pharyngolaryngeal region. The treatments include open and endoscopic surgery; intraoperative bleeding is often troublesome. Angiolytic lasers such as the potassium titanyl phosphate (KTP) laser enable photocoagulation for such hemorrhagic lesions without bleeding; we report findings from a series of adult patients.

Methods: Seven adults were treated with a KTP laser set at a low power of 1.5 W in continuous mode. Photocoagulation was easily performed for shallow lesions; however, laser irradiation of bulky venous malformations resulted only in surface photocoagulation. In such cases, the crust remaining after photocoagulation was removed, and laser energy was repeatedly delivered until no remnant lesion was seen. An office procedure using flexible endoscopy was performed under topical anesthesia for 1 patient with a limited lesion.

Results: The lesions were well controlled in all cases without major complications. A patient with a large obstructing lesion had a relapse. Because the recurrent lesion is small and the patient does not desire additional treatment at this time, she is being observed carefully.

Conclusions: Photocoagulation using the KTP laser is a feasible and relatively safe treatment for pharyngolaryngeal venous malformations in adults.

Key Words: adult pharyngolaryngeal venous malformation, KTP laser, photocoagulation therapy, potassium titanyl phosphate laser.

INTRODUCTION

Vascular anomalies are common in the head and neck region. They usually manifest as subglottic lesions in infants, whereas venous malformations in adults are rare in the pharyngolaryngeal region. Most venous malformations in adults do not progress, and small malformations can be observed without the need for aggressive treatments. Aggressive treatments are needed in case of bleeding, airway obstruction, or involvement of the digestive tract.

Many types of treatments have been reported, including systemic or local steroids, radiotherapy, and surgery.¹ Although all therapies have had some success, in the end, only surgery has become popularly used because of its certainty and relative safety.

The surgical treatments include both open and endoscopic surgery. In open surgery, lesions are accessed through pharyngotomy or laryngofissure. Considering intraoperative and postoperative mor-

bidity, this approach is recommended only for extended pharyngolaryngeal venous malformations. On the other hand, endoscopic surgery is the more popular and preferred method because of its minimal invasiveness. However, because of the limited surgical field, intraoperative bleeding is often troublesome.

Recent advances in technology have allowed the use of lasers as an option in endoscopic surgery, and various lasers have been reported as part of the treatment of pharyngolaryngeal venous malformations. The potassium titanyl phosphate (KTP) laser has recently attracted the most attention because of its coagulation ability.

Since 1992, we have treated adults with pharyngolaryngeal venous malformations by use of photocoagulation therapy with the KTP laser. The KTP laser is preferentially absorbed by hemoglobin and enables photocoagulation for such hemorrhagic le-

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PATIENT DATA

Sex	Age (y)	Site	Initial Symptom	Anesthesia	Inpatient or Outpatient	Blood Loss	Duration of Procedure (min)	Preoperative Tracheotomy	Remnant or Relapse	Follow-Up Period (mo)
F	27	FVF, PWPG, PS	Discomfort	General	Inpatient	Little	100	+	—	3
F	45	Arytenoid	Asymptomatic	General	Inpatient	Little	145	+	—	12
M	46	Arytenoid, PS	Asymptomatic	Topical	Outpatient	Little	10	—	—	15
M	55	Arytenoid, PS	Discomfort	General	Inpatient	Little	22	—	—	12
M	71	PS, aryepiglottic fold	Asymptomatic	General	Inpatient	Little	44	—	—	12
F	77	Arytenoids, PS	Discomfort	General	Inpatient	Little	30	—	+	4
F	55	PS	Discomfort	General	Inpatient	Little	5	—	—	6

FVF — false vocal fold; PWPG — posterior wall of posterior glottis; PS — pyriform sinus.

sions without bleeding. Here, we report the findings for a series of 7 adults with pharyngolaryngeal venous malformations treated with photocoagulation therapy using the KTP laser. We examine the method's usefulness and safety and discuss how the laser should be used in the management of pharyngolaryngeal venous malformations.

MATERIALS AND METHODS

Patients. Clinical information for all 7 patients is summarized in the Table. The 7 adults (3 men, 4 women) with pharyngolaryngeal venous malformations were treated with endoscopic surgery using the KTP laser in 1992 to 2007 at Kyoto Medical Center and Kyoto University Hospital. Their ages ranged from 27 to 77 years (average, 53.7 years). The patients, except for case 3, were observed as inpatients, and the postoperative follow-up ranged from 3 to 15 months. The lesion involved the pyriform sinus in 6 of the 7 patients and the arytenoid cartilages in 4 of the 7 patients. Three of the 7 patients were asymptomatic; however, photocoagulation was performed to prevent possible bleeding.

Surgical Procedure. In 6 of the 7 patients, photocoagulation of the pharyngolaryngeal lesions was performed under general anesthesia. Tracheotomy was performed before surgery in 2 patients (cases 1 and 2) to prevent respiratory trouble due to postoperative edema. The glottis was exposed with a direct laryngoscope: either a Zeitel's Universal Modular Glottiscope (Endocraft Co, Boston, Massachusetts) or a Kleinsasser laryngoscope (Karl Storz GmbH and Co, Tuttlingen, Germany). Pharyngolaryngeal lesions were photocoagulated with a KTP laser (Laserscope, San Jose, California) set at low power (1.5 W) with a defocused beam in continuous mode. During photocoagulation, the laser was delivered to the lesion through a flexible optical fiber attached to a curved handpiece with a suction channel for evacuating smoke. The beam was delivered from just above the surface of the lesion, and the tip of the fi-

ber never contacted the lesion. For 1 patient (case 3) with a limited lesion, the procedure was performed via flexible endoscopy under topical anesthesia in an office setting.

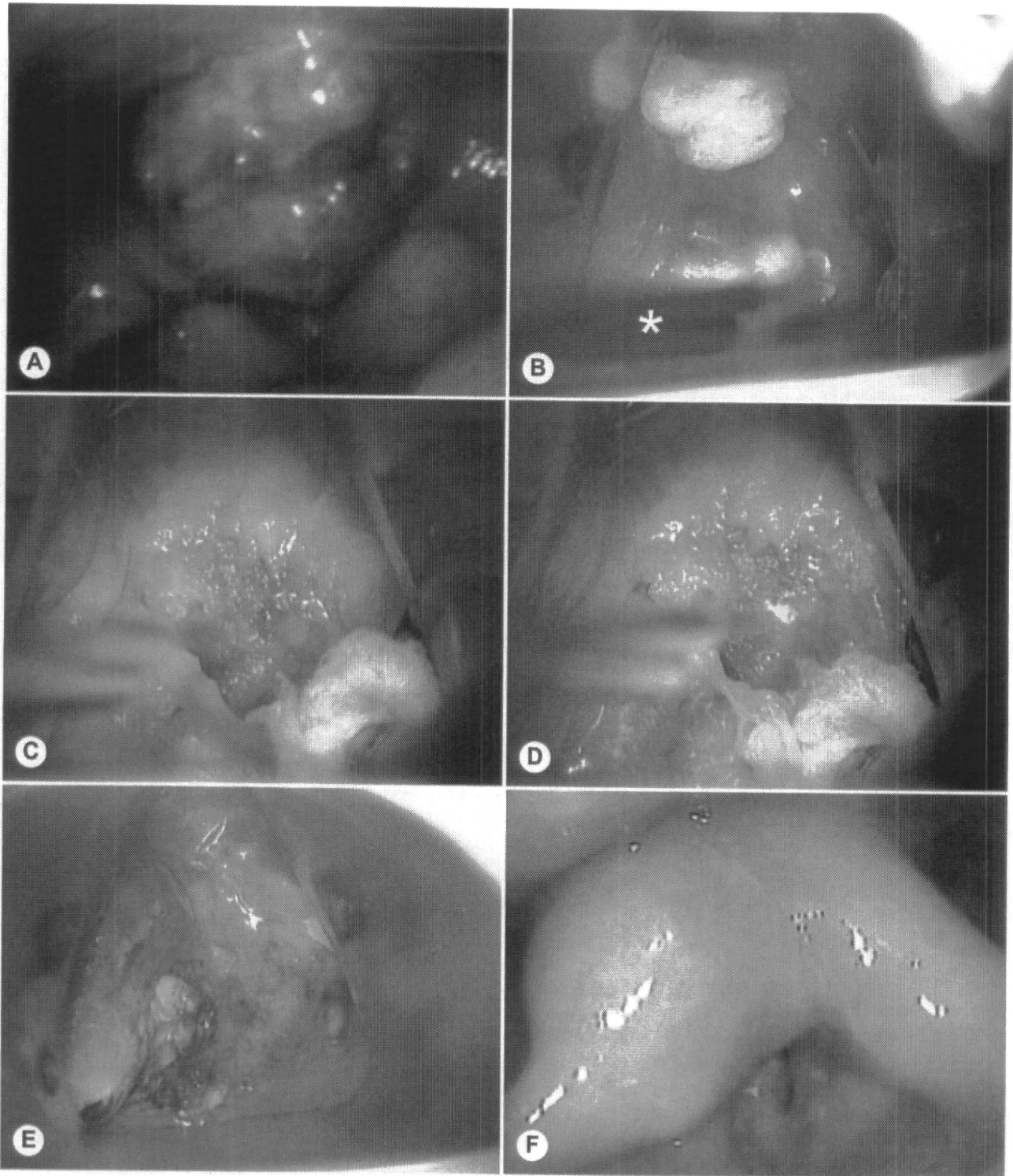
RESULTS

Intraoperative Findings During Photocoagulation. The laser irradiation was simple and relatively safe; photocoagulation was easily performed for all patients without any complication. At a low power level of 1.5 W, the laser beam is well absorbed by hemoglobin in the underlying vascular lesion, resulting in minimal damage to surrounding tissues.²

The Figure shows a typical photocoagulation of a bulky venous malformation with the KTP laser (case 6). In this case, the lesion involved the arytenoid cartilages and pyriform sinuses. At first, the laser irradiation resulted in photocoagulation of the surface only. As the surface was photocoagulated, the lesion shrank and the surface became covered with crust. The crusts were debrided, after which the laser energy was repeatedly delivered to the exposed lesion until the remnant lesion disappeared. Repeated laser irradiation was easily performed without complications. Also, when there was a network of vessels around the venous malformation, they were photocoagulated to prevent relapse. This step caused shrinkage of the vessels; no refilling was observed after photocoagulation.

As shown in the Table, the amount of intraoperative bleeding was very small in all cases. In the initial 2 cases, because we were not used to the procedure, the photocoagulation took much more time. From the third case, the duration of the procedure became significantly shorter.

Postoperative Course. There were neither remnants nor relapses, except in 1 patient (case 6). This patient, who had a bulky pharyngolaryngeal venous malformation, presented with a small remnant lesion at the pharyngoesophageal junction 3 months after surgery. The patient, however, has been observed



(Case 6) Photocoagulation of bulky venous malformation under direct microlaryngoscopy. **A)** Preoperative findings of venous malformation on arytenoid cartilages and pyriform sinuses. **B)** Laser irradiation resulted in photocoagulation of surface and shrinkage of lesion. Asterisk — handpiece of laser. **C)** Post-photocoagulated crusts were scraped out. **D)** Laser energy was repeatedly delivered to underlying lesion. **E)** Photocoagulation was completed with no remnant lesion. **F)** Postoperative findings at 1 month after surgery indicated that lesion mostly disappeared.

without further treatments to date, because she has no symptoms and does not want further intervention. All patients became asymptomatic. No postoperative complications, such as bleeding, respiratory

troubles, or scar formation, occurred.

DISCUSSION

Vascular anomalies are common in the head and

neck. Especially in the pharyngolaryngeal region, they often manifest as subglottic mucosal-covered lesions in infants. Lesions in this region are rarely encountered in adults. Histologically, anomalies in infants are of the capillary type with tangled nests of small vessels. Anomalies in adults, on the other hand, are of the cavernous or mixed type with thin, fragile mucosa overlying the vascular stroma.³

In the pharyngolaryngeal region, the clinical signs relate to the size and location of the lesion. Patients with small pharyngolaryngeal venous malformations usually have no symptoms, and they can be managed conservatively without aggressive treatments. However, large venous malformations cause various symptoms, such as hoarseness, cough, foreign body sensation, and dysphagia. Further treatments are needed in cases with bleeding, airway obstruction, or involvement of the digestive tract.

Treatment of venous malformations is challenging, and results have been reported for various kinds of treatments. As mentioned above, endoscopic laser surgery has been generally accepted and has become a popular therapeutic modality. Many reports describe the use of various kinds of lasers, such as the carbon dioxide (CO₂) laser,^{4,5} the neodymium:yttrium aluminum-garnet (Nd:YAG) laser,⁶ and the KTP laser.⁷ However, the appropriate use of lasers for pharyngolaryngeal venous malformations in adults is still controversial, because only case reports or limited case series are currently available.

Since Simpson et al⁴ first reported CO₂ laser therapy for subglottic vascular anomalies in 1979, the CO₂ laser has been used frequently in the management of pharyngolaryngeal vascular anomalies. It has a wavelength of 10,600 nm in the invisible light range and requires an aiming beam during operation. The beam of this laser is well absorbed by tissues with a high water content without tissue penetration, and therefore CO₂ laser cauterization is less effective in hemostasis.⁷ Lucioni et al⁵ treated 6 cases of supraglottic adult vascular anomalies using a CO₂ laser and reported intraoperative bleeding complications in 3 cases. Postoperative scarring caused by CO₂ laser therapy often becomes a severe problem, especially when the scarring involves the subglottic region.

The Nd:YAG laser has a wavelength of 1,064 nm in the invisible light range and also requires an aiming beam.³ This laser can be delivered through optic fibers and is easy to handle. This wavelength is more readily absorbed in blood than in surrounding tissue.⁸ The emitted laser therefore has a deep coagulation effect, whereas the damage to the overlying watery mucosa is minimal. However, there

is significant risk of transmural injury and a risk of scar formation. Nicolai et al⁹ compared CO₂ laser therapy with Nd:YAG laser therapy for subglottic vascular anomalies and concluded that the former is superior to the latter in terms of postoperative complications.

The KTP laser has a wavelength of 532 nm in the visible light range and emits bright-green laser light.¹⁰ This laser is produced by a crystal of KTP (potassium titanyl phosphate), doubling the frequency of the Nd:YAG laser. It does not require an aiming beam and can be delivered through optic fibers. Because the wavelength is near the absorption peak of hemoglobin, the laser energy is preferentially absorbed by hemoglobin molecules and therefore has deeper penetration of tissue and a deeper coagulation effect than those of the CO₂ laser. Irradiation with this laser is thought to be effective in treatment of hemorrhagic lesions such as vascular anomalies. Although excessive irradiation with this laser causes transmural injury, it has a lower risk of thermal damage to surrounding tissue than does the Nd:YAG laser. Kacker et al¹¹ treated 8 patients with subglottic vascular anomalies using the KTP laser, and because of its characteristics and system, they concluded that the KTP laser represents an improvement over the CO₂ laser in treating subglottic vascular anomalies. In addition, to prevent postoperative deterioration of the mucosal wave due to scarring, it is important to preserve as much of the normal tissue as possible when treating microvascular lesions of the vocal fold. Hirano et al¹⁰ treated 12 cases of microvascular lesions of the vocal fold using the KTP laser (set at a low power) without adverse effects and concluded that KTP laser photocoagulation therapy is a relatively safe method for treating microvascular lesions of the vocal fold.

In our case series, there were no problems associated with KTP laser therapy in terms of bleeding or scar formation. As shown in the Figure, even a bulky venous malformation was photocoagulated with minimum bleeding; the surgical view was never hampered. In 2 patients with a bulky venous malformation, we performed tracheotomy before surgery; however, the postoperative edematous changes were minimal. Thus, tracheotomy is not always necessary. In addition, we were able to treat 1 patient with a small venous malformation with photocoagulation therapy using flexible endoscopy in the office under topical anesthesia. For patients with small venous malformations, this method seems to be ideal in terms of the burden on the patients. Although 1 patient with a bulky venous malformation presented later with a small remnant lesion, she has been observed without further treatment, because no