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Role of Reflux in Tracheoesophageal Fistula Problems After Laryngectomy

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Objectives: The purpose of this 2-year prospective nonrandomized study was to investigate the relationship between pathological supraesophageal reflux and the occurrence of speech fistula complications, especially severe fistula enlargement, in patients who underwent total laryngectomy and prosthetic voice restoration.

Methods: We objectively assessed the presence of reflux disease using 24-hour dual-probe pH monitoring in 60 laryngectomized patients, correlated the incidence of tracheoesophageal fistula complications with the severity of reflux, and assessed the risk of problems by determining the absolute number of reflux events at the level of the speech fistula, the reflux area index score, and the DeMeester score.

Results: All patients with fistula enlargement showed highly pathological results in the diagnostic tests for reflux disease. Depending on reflux severity, the relative risk of developing fistula complications was up to 10 times higher for these patients.

Conclusions: We found a significant correlation between the occurrence of tracheoesophageal fistula complications and the severity of supraesophageal reflux. Potential chronic irritation of the esophageal and tracheal mucosa can possibly contribute to the development of these problems. If the presence of reflux disease has been confirmed by 24-hour dual-probe pH monitoring, patients with fistula complications should be treated with proton pump inhibitors.

Key Words: complication, pH monitoring, reflux, tracheoesophageal fistula, voice rehabilitation.

INTRODUCTION

Apart from tumor control, voice rehabilitation is a primary therapeutic objective in patients undergoing total laryngectomy. In the past 20 years, the use of a voice prosthesis that is inserted into a tracheoesophageal fistula has become the treatment of choice for the restoration of speech. The placement of a voice prosthesis is not only a simple surgical procedure, but also an easy and rapid method of voice rehabilitation. It is associated with an excellent success rate of 85% to 95% and a low rate of complications.[1-4] Serious complications have been reported only in rare cases.[1,4] Far more common are minor complications such as crusting, fungal growth, the formation of granulation tissue leading to poor phonation, transprosthetic or periprosthetic leakage, and substantial enlargement of the tracheoesophageal fistula.[3-5] Whereas minor problems such as crust formation in the region of the speech valve, fungal growth, granulation tissue formation, and transprosthetic leakage can be resolved simply by replacing the speech valve, a periprosthetic leakage or a substantial enlargement of the tracheoesophageal fistula can be a more demanding challenge for the attending physician.

Increased granulation tissue formation and tracheoesophageal fistula enlargement can lead not only to a loss of the ability to phonate, but also to a loss of the prosthesis, and sometimes severe and life-threatening aspiration symptoms.[4,6] For this reason, effective management of fistula problems is extremely important in order not only to maintain the patient's ability to communicate but also to prevent adverse effects on the overall prognosis and quality of life.[7]

Because 2 of our patients showed a substantial delay in wound healing and a persistent fistula with severe reflux after the surgical closure of a tracheoesophageal fistula with a pedicled muscle flap,[8] we conducted a prospective study in order to investigate the relationship between the presence of reflux disease and the incidence of tracheoesophageal fistula complications.

PATIENTS AND METHODS

From March 2006 to November 2008, a total of

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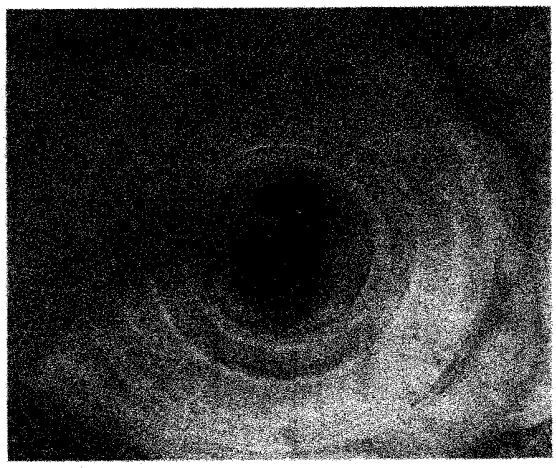
TABLE 1. CHARACTERISTICS OF STUDY PARTICIPANTS

Patient Characteristics	*No. of Patients*
Gender	
Male	52
Female	8
Age	
Mean	64.7 ± 7.8 y
Range	40-81 y
Follow-up period	
Mean	4.4 ± 3.7 y
Range	2-9 y
Radiotherapy	
Postoperative radiotherapy	44
No radiotherapy	16
Periprosthetic leakage	
Yes	29
Atrophy	11
Enlargement (9-15 mm)	11
Enlargement (>15 mm)	7
No. of patients	31

60 laryngectomized patients (8 women, 52 men) took part in this study after having given their written informed consent. The study had been approved by the ethics committee of the University of Ulm (Ref. 06/2006). The patients were randomly selected from a total of approximately 110 laryngectomees who were using a tracheoesophageal voice prosthesis and were attending the Oncology Service of the German Armed Forces Hospital in Ulm. The mean (±SD) age of the patients was 64.7 ± 7.8 years (range, 40 to 81 years). The mean time between laryngectomy and inclusion in the study was 4.4 ± 3.7 years.

All patients had primarily undergone voice restoration with a Provox I prosthesis. At the beginning of the study, 58 patients used a Provox II prosthesis and 2 patients used a Provox Activalve prosthesis. Twenty-nine of the 60 patients (48%) reported tracheoesophageal fistula complications such as recurrent periprosthetic leakage (more than 3 times) caused by substantial fistula enlargement or atrophy of the membranous wall of the trachea. The mean time between laryngectomy and the first occurrence of periprosthetic leakage was 698 ± 256.2 days.

In 18 of the 29 patients, the fistula was enlarged to a diameter of more than 9 mm. Seven patients presented with an enlargement to more than 15 mm. Eleven patients had a fistula that was enlarged to a diameter between 9 and 15 mm and was managed more than 3 times by soft tissue augmentation with siloxanes (Vox Implant), silicone washers, or oversewing. Eleven further patients showed marked atrophy of the membranous wall of the trachea and



Measurement of speech fistula diameter using gum elastic bougies of different sizes.

continuous periprosthetic leakage with a fistula diameter of less than 9 mm (Table 1).

Forty-four patients received postoperative radiotherapy (64 to 70 Gy) to the primary tumor site and irradiation (54 Gy) of the lymphatic drainage pathways. No patient underwent preoperative radiotherapy or chemotherapy.

After having obtained fully informed written consent from the patients, we conducted a thorough photographic documentation and measured fistula diameters at the beginning of our study. We measured the diameter of a fistula by inserting gum elastic bougies of different sizes after having removed the voice prosthesis. For this purpose, we used gum elastic bougies (Rüsch, Kernen, Germany) in sizes from 8 to 20 mm in 1-mm increments. In patients with oval-shaped fistulas, we additionally used narrow strips of millimeter paper to measure the size of the fistula. The largest diameter of each fistula was used in our study (see Figure).

The membranous wall of the trachea has a mean thickness of approximately 8 mm. Atrophy was assumed when the wall was reduced by 60% of its normal thickness (3.2 mm). We measured tracheal wall thickness using a Provox sizer (Atos Medical, Hörby, Sweden). Atrophy was also assumed when a 4.5-mm Provox II prosthesis had a play of more than 1 mm in the region of the shaft.

We objectively assessed the presence of reflux by 24-hour pH monitoring (Digitrapper, Medtronic Xomed, Jacksonville, Florida) using catheters with 2 pH sensors spaced 10 cm apart (VersaFlex, Promedia Medizintechnik, Siegen, Germany). The patients were advised on how to use the measuring system. The catheters were introduced transnasally under surface anesthesia and advanced until pH val-

TABLE 2. DIVISIONS INTO PATIENT GROUPS

Division Scheme	*Groups*	*Range of Parameter*	*No. of Patients*	*Mean ± SD*	*Median*
Reflux area index score*	Group 1	<6.3	8	1.41 ± 1.49	1
	Group 2	6.4-50	16	24.11 ± 13.41	22
	Group 3	51-250	19	106.42 ± 56.58	86.5
	Group 4	>250	17	780.32 ± 778.37	423.2
No. of reflux events†	Group 1	0-6 events	4	1 ± 2	0
	Group 2	7-25 events	16	16.93 ± 4.52	17
	Group 3	26-100 events	22	55.22 ± 22.51	53.5
	Group 4	>100 events	18	259.65 ± 184.24	171
DeMeester score‡	Group 1	<14.75	18	6.9 ± 4.52	6.25
	Group 2	14.75-50	25	29.04 ± 11.24	23.6
	Group 3	>50	17	259.05 ± 81.57	77.05

*Division of patients into 4 groups according to reflux area index. Reflux area index score of less than 6.3 is considered to be normal in healthy population.

†Division of patients into 4 groups according to number of reflux events in region of tracheoesophageal fistula. Six or fewer reflux events is considered to be normal in healthy population.

‡Division of patients into 3 groups according to DeMeester score as measure of severity of reflux. DeMeester score of less than 14.75 is defined as normal in healthy population.

ues below 7 were measured at both measurement sites. They were then withdrawn until a pH value higher than 7 was recorded. In addition, transnasal flexible endoscopy was performed to ensure that the upper measurement site (marked in black) was at the level of the tracheoesophageal fistula. The pH values were registered every 4 seconds over a period of 24 hours. The patients used event buttons on the recording unit to indicate mealtimes and to record time spent lying down. Moreover, they filled out an event diary by hand. All values were recorded and analyzed with PolygramNet software (Medtronic Xomed). We determined the number of reflux episodes in terms of pH drops below 4 in the distal and proximal esophagus, the reflux area index (RAI) score at a pH level of less than 4, and the DeMeester score. In the literature, an RAI score of less than 6.3 is considered to be normal in a healthy population.[9,10] Since reflux episodes in the region of the upper esophagus and the distal pharynx are briefer in duration and fewer in frequency than those in the region of the distal esophagus, the usual reflux parameters and scores are of limited usefulness for these sites. An RAI score of 4 is the reflux area under the curve for all episodes with a pH of less than 4 recorded during a specific time interval divided by the duration of the time interval. It thus reflects not only the absolute number of proximal reflux events, but also the duration and severity of pH drops. An RAI score of higher than 6.3 is likely to be indicative of supraesophageal reflux. In addition, this index has the advantage that all artifacts and meal periods plus 3 minutes of postprandial time can be excluded from analysis so that values for actual reflux episodes are obtained. Moreover, we reviewed the measurement results "by hand" in order to rule out pseudoreflux events in the region of the upper measurement site. We also analyzed the absolute number of reflux events, which is an established parameter in the diagnosis of reflux. Six or fewer supraesophageal or extraesophageal reflux events per 24 hours is considered to be normal in a healthy population.[11,12]

DeMeester scores were calculated during the entire 24 hours of pH monitoring on the basis of reflux events defined by a pH value below 4. In this study, DeMeester scores must be evaluated with caution, because the location of the lower measurement site was determined not by manometry, but on the basis of pH values. Since the DeMeester score is still commonly used in defining reflux disease, we also placed our patients into groups according to their DeMeester scores. A DeMeester score of less than 14.75 is regarded as normal in a healthy population.

The patients were divided into 4 groups depending on their number of reflux episodes at the level of the fistula and their RAI score and into 3 groups depending on their DeMeester score. The groups were then analyzed for the frequency of fistula complications and the relative risk (RR) for the occurrence of complications (Table 2). We obtained the normal values for the RAI, the absolute number of reflux events, and the DeMeester score from the literature. Other relevant values are based on an earlier study that we performed on patients without tumors who had otolaryngological conditions and reflux-associated symptoms. We performed 24-hour pH monitoring in 50 patients and correlated the severity of otolaryngological symptoms (reflux finding score) with the severity of reflux assessed by 24-hour pH

TABLE 3. ABSOLUTE AND RELATIVE NUMBERS OF FISTULA COMPLICATIONS IN RELATION TO ABSOLUTE NUMBER OF SUPRAESOPHAGEAL REFLUX EVENTS AS PARAMETER OF SEVERITY OF REFLUX

Type of Fistula Complication	*Statistical Data*	*Group 1 (0-6 Events)*	*Group 2 (7-25 Events)*	*Group 3 (26-100 Events)*	*Group 4 (>100 Events)*
Periprosthetic leakage (n = 29)	No. of complications	25% (1/4)	25% (4/16)	36% (8/22)	88% (16/18)
	Relative risk		1	1.558	3.52
	95% confidence interval		0.1320 to 7.574	0.1917 to 13.160	1.337 to 77.833
	p		NS	NS	0.0239
Atrophy of membranous wall of trachea (n = 11)	No. of complications	25% (1/4)	6% (1/16)	14% (3/22)	33% (6/18)
	Relative risk		0.3	0.54	1.4
	95% confidence interval		0.05916 to 1.878	0.07402 to 4.019	0.1752 to 11.187
	p		NS	NS	NS
Fistula enlargement of 9-15 mm (n = 11)	No. of complications	25% (1/4)	12.5% (2/16)	14% (3/22)	28% (5/18)
	Relative risk		0.53	0.55	1.12
	95% confidence interval		0.07903 to 3.546	0.07402 to 4.019	0.1434 to 8.827
	p		NS	NS	NS
Fistula enlargement of >15 mm (n = 7)	No. of complications	25% (1/4)	17.5% (3/16)	18% (4/22)	55% (10/18)
	Relative risk		0.75	0.7	3.0
	95% confidence interval		0.1035 to 5.436	0.09262 to 5.508	0.3660 to 24.590
	p		NS	NS	0.586
Granulation tissue formation (n = 12)	No. of complications	25% (1/4)	25% (4/16)	32% (7/22)	0% (0/18)
	Relative risk		1	1.3	0.14
	95% confidence interval		0.1320 to 7.574	0.1625 to 10.942	0.05010 to 0.4074
	p		NS	NS	0.1818

Table also gives relative risk of occurrence of various fistula complications, together with confidence interval. Relative risk was determined by comparing group 1 with groups 2, 3, and 4 by use of 2 × 2 contingency tables. Value of p was calculated with Fisher's exact test.

NS — not significant.

monitoring. We were thus able to assign an increase in reflux values to a corresponding level of reflux severity. These findings were transferred to tumor patients.

In addition, patients who presented with a fistula enlargement that required treatment (n = 18) were compared with patients without fistula enlargement (n = 42) in terms of the number of reflux episodes, the RAI score, and the DeMeester score.

The group with periprosthetic leakage included all patients who experienced periprosthetic leakage as a result of either fistula enlargement (18 patients) or atrophy of the membranous wall of the trachea (11 patients). For a more precise classification, we divided the 18 patients with fistula enlargement into groups with a fistula diameter of 9 to 15 mm (11 patients) and with severe fistula enlargement (greater than 15 mm; 7 patients). The occurrence of 1 or 2 discrete periprosthetic leakage events after the insertion of a voice prosthesis was considered to be normal.

Excel (Microsoft, Seattle, Washington) and InStat 3.06 (Graphpad Software, San Diego, California) were used for statistical analysis. Depending on reflux disease severity, we divided the patients into groups according to the number of reflux episodes, the RAI score, and the DeMeester score in order to assess whether reflux promotes the occurrence of fistula enlargement. The RR of fistula complications was determined for the various patient groups. The RR, 95% confidence interval (CI), and p value were calculated from 2 × 2 contingency tables and Fisher's exact test.

When the distribution was not normal, a Mann-Whitney test was used to compare patients with severe fistula enlargement to patients without fistula enlargement. The probability of error threshold was a p value of less than 0.05.

We performed both univariate and multivariate regression analyses in order to investigate whether radiotherapy influenced fistula-related complications. Analysis included both reflux disease and radiotherapy. We used the SPSS 18 Regression Models module. The severity of periprosthetic leakage was the dependent variable, and the severity of reflux and radiotherapy were the independent variables.

RESULTS

When the patients were divided into 4 groups depending on the number of reflux events (see Table 2 for definitions of groups), there was a significant increase in the occurrence of periprosthetic leakage

TABLE 4. ABSOLUTE AND RELATIVE NUMBERS OF FISTULA COMPLICATIONS IN RELATION TO REFLUX AREA INDEX SCORE AS PARAMETER OF SEVERITY OF REFLUX

Type of Fistula Complication	*Statistical Data*	*Group 1 (Score of <6.3)*	*Group 2 (Score of 6.4-50)*	*Group 3 (Score of 51-100)*	*Group 4 (Score of >100)*
Periprosthetic leakage (n = 29)	No. of complications	25% (2/8)	37.5% (6/16)	58% (11/19)	64% (11/17)
	Relative risk		1.5	2.7	3.2
	95% confidence interval		0.3861 to 5.827	0.6792 to 11.426	0.8054 to 13.115
	p		NS	NS	NS
Atrophy of membranous wall of trachea (n = 11)	No. of complications	0% (0/8)	19% (3/16)	11% (2/19)	35% (6/17)
	Relative risk		1.4	0.87	2.7
	95% confidence interval		0.2315 to 8.468	0.1570 to 4.876	0.1732 to 0.6426
	p		NS	NS	NS
Fistula enlargement of 9-15 mm (n = 11)	No. of complications	12.5% (1/8)	12.5% (2/16)	26% (5/19)	18% (3/17)
	Relative risk		1	2.0	1.44
	95% confidence interval		0.1806 to 5.536	0.3024 to 13.227	0.2199 to 8.085
	p		NS	NS	NS
Fistula enlargement of >15 mm (n = 7)	No. of complications	12.5% (1/8)	0% (0/16)	21% (4/19)	12% (2/17)
	Relative risk		0.3	1.6	0.95
	95% confidence interval		0.1640 to 0.5646	0.2484 to 10.191	0.1720 to 5.297
	p		NS	NS	NS
Granulation tissue formation (n = 12)	No. of complications	12.5% (1/8)	25% (4/16)	21% (4/19)	17% (3/17)
	Relative risk		1.8	1.6	1.3
	95% confidence interval		0.2897 to 11.712	0.2484 to 10.191	0.2199 to 8.085
	p		NS	NS	NS

Table also gives relative risk of occurrence of various fistula complications, together with confidence interval. Relative risk was determined by comparing group 1 with groups 2, 3, and 4 by use of 2 × 2 contingency tables. Value of p was calculated with Fisher's exact test.

from at least 25% in groups 1 to 3 to 88% in group 4. Likewise, the occurrence of atrophy of the membranous wall of the trachea increased from 25% in group 1 to 33% in group 4. In addition, there was a rise in the occurrence of fistula enlargement (9 to 15 mm) from 25% in group 1 to 28% in group 4. The occurrence of severe fistula enlargement (greater than 15 mm) increased from 25% in group 1 to 55% in group 4. The RR of the occurrence of periprosthetic leakage increased to 1.558 (95% CI, 0.1917 to 13.160) for group 3 and 3.52 (95% CI, 1.337 to 77.833) for group 4 (p = 0.0239) when compared with group 1. A comparison of groups 1 and 4 showed that the RR of atrophy of the membranous wall of the trachea increased to 1.4 (95% CI, 0.1752 to 11.187) and the RR of fistula enlargement to 1.12 (95% CI, 0.1434 to 8.827) for patients with a fistula diameter of 9 to 15 mm and to 3.0 (95% CI, 0.3660 to 24.590) for patients with severe fistula enlargement (greater than 15 mm). For all patients with fistula enlargement, the RR was 1.8 in group 3 (47%) and 1.2 in group 4 (30%; Table 3).

When the patients were divided into 4 groups depending on the RAI score (see Table 2 for definitions of groups), the occurrence of periprosthetic leakage and atrophy of the membranous wall of the trachea increased with a higher RAI score. The occurrence of periprosthetic leakage increased from 25% in group 1 to 64% in group 4. The occurrence of atrophy increased from 0% in group 1 to 35% in group 4, and that of fistula enlargement from 12.5% in group 1 to 26% in group 3 for patients with a fistula enlargement to 9 to 15 mm (Table 4).

The RR for the development of periprosthetic leakage increased with a higher RAI score and was 3.2 for group 4 (95% CI, 0.8054 to 13.115; p value was not significant). The RR of atrophy increased to 1.4 (95% CI, 0.2315 to 8.468) for group 2 and 2.7 for group 4 (95% CI, 0.1732 to 0.6426; p value was not significant), and the RR of fistula enlargement (9 to 10 mm) rose to 2.0 (95% CI, 0.3024 to 13.227) for group 3 and 1.44 (95% CI, 0.2199 to 8.085) for group 4. The RR for all patients with fistula enlargement was 1.6 in group 4 (83%; Table 4).

When the patients were divided into 3 groups according to their DeMeester scores (see Table 2 for definitions of groups), the occurrence of the various fistula complications again increased with higher scores. The occurrence of periprosthetic leakage rose from 16.7% in group 1 to 76% in group 3 (RR, 4.2; 95% CI, 1.479 to 11.988; p = 0.006). The occurrence of atrophy of the membranous wall of the trachea increased from 5.6% in group 1 and 16% in group 2 (RR, 1.7; 95% CI, 0.3076 to 9.884) to 29% in group 3 (RR, 3.5; 95% CI, 0.5724 to 21.612).

TABLE 5. ABSOLUTE AND RELATIVE NUMBERS OF FISTULA COMPLICATIONS IN RELATION TO DEMEESTER SCORE AS PARAMETER OF SEVERITY OF REFLUX

Type of Fistula Complication	*Statistical Data*	*Group 1 (Score of <14.75)*	*Group 2 (Score of 14.76-50)*	*Group 3 (Score of >50)*
Periprosthetic leakage (n = 29)	No. of complications	16.7% (3/18)	52% (13/25)	76% (13/17)
	Relative risk		2.9	4.2
	95% confidence interval		1.012 to 8.678	1.479 to 11.988
	p		0.0261	0.006
Atrophy of membranous wall of trachea (n = 11)	No. of complications	5.6% (1/18)	16% (3/25)	29% (5/17)
	Relative risk		1.7	3.5
	95% confidence interval		0.3076 to 9.884	0.5724 to 21.612
	p		NS	NS
Fistula enlargement of 9-15 mm (n = 11)	No. of complications	5.6% (1/18)	24% (6/25)	23% (4/17)
	Relative risk		3.3	2.8
	95% confidence interval		0.5210 to 20.972	0.4772 to 16.821
	p		NS	NS
Fistula enlargement of >15 mm (n = 7)	No. of complications	5.6% (1/18)	12% (3/25)	23% (4/17)
	Relative risk		1.7	2.8
	95% confidence interval		0.3076 to 9.884	0.4772 to 16.821
	p		NS	NS
Granulation tissue formation (n = 12)	No. of complications	33.3% (6/18)	20% (5/25)	6% (1/17)
	Relative risk		0.7	0.5
	95% confidence interval		0.3411 to 1.386	0.2961 to 0.8443
	p		NS	NS

Table also gives relative risk of occurrence of various fistula complications, together with confidence interval. Relative risk was determined by comparing group 1 with groups 2 and 3 by use of 2 × 2 contingency tables. Value of p was calculated with Fisher's exact test.

Likewise, the occurrence of fistula enlargement (9 to 15 mm) rose from 5.6% in group 1 to 24% in group 2 (RR, 3.3; 95% CI, 0.5210 to 20.972; p value was not significant) and 23% in group 3 (RR, 2.8; 95% CI, 0.4772 to 16.821; p value was not significant). In the group of patients with fistula enlargement, the RR was thus 3.2 for group 2 and 4.2 for group 4 (Table 5).

A comparison of the 18 patients with substantial fistula enlargement and recurrent periprosthetic leakage with the other patients showed that reflux disease was considerably more severe in patients with fistula enlargement than in patients without fistula enlargement. This finding is reflected in the absolute numbers of reflux episodes (71.9 versus 162.2; p = 0.001), the DeMeester scores (37.5 versus 108.3; p = 0.004), and the RAI scores (114.1 versus 327.1; p = 0.005; Table 6).

An analysis of the influence of supraesophageal reflux on prosthesis life span showed that the mean device life span was 99.1 ± 34.0 days (median, 102 days) in patients with reflux symptoms and 254.9 ± 79.7 days (median, 221 days) in patients without reflux. More specifically, the mean life span of prostheses was 263.3 ± 93.5 days (median, 232 days) in patients without reflux symptoms and without periprosthetic leakage (the reason for replacement was transprosthetic leakage in these cases) and 187.4 ± 67.3 days (median, 179 days) in patients with reflux symptoms and without periprosthetic leakage. The mean device life span was 48.4 ± 23.4 days (median, 44 days) in patients with reflux and

TABLE 6. COMPARISON OF PATIENTS WITH FISTULA ENLARGEMENT OF >9 MM (N = 18) AND PATIENTS WITHOUT FISTULA ENLARGEMENT (N = 42) IN RELATION TO MEASURED REFLUX PARAMETERS

	Supraesophageal Reflux Events		*DeMeester Score*		*Reflux Area Index Score*	
	No Enlargement	*Enlargement*	*No Enlargement*	*Enlargement*	*No Enlargement*	*Enlargement*
Mean	71.9	162.2	37.5	108.3	114.1	327.1
SD (±)	86.8	144.3	56.6	85.4	138.1	419.3
Median	35	96	22.6	104.7	68.7	196
p	0.001		0.004		0.005	

Level of significance was calculated with Mann-Whitney test (significance at 95% level).

TABLE 7. PROVOX II PROSTHESIS LIFE SPAN IN PRESENCE OR ABSENCE OF REFLUX

	Prosthesis Life Span With Reflux (d)		*Prosthesis Life Span Without Reflux (d)*		
	Mean ± SD	*Median*	*Mean ± SD*	*Median*	*p*
All patients	99.1 ± 34.0	102	254.9 ± 79.7	221	0.001
Patients with transprosthetic leakage	187.4 ± 67.3	179	263.3 ± 93.5	232	0.05
Patients with periprosthetic leakage	48.4 ± 23.4	44	79.5 ± 49.2	81	0.01

Statistical significance was determined with Mann-Whitney test. Probability of error threshold was p value of less than 0.05.

periprosthetic leakage and 79.5 ± 49.2 days (median, 81 days) in patients with periprosthetic leakage and without reflux (Table 7).

There was no difference between patients with reflux and patients without reflux in the formation of biofilms or the growth of *Candida* species on prosthesis surfaces. Three patients (1 with a fistula enlarged to more than 15 mm and 2 with fistulas enlarged to less than 15 mm) with periprosthetic leakage showed a stenosis from scar tissue formation in the region of the pharyngoesophageal segment and an increased flow rate in the region of the speech fistula.

Minor periprosthetic leakages were seen in 8 of the 44 patients (18.2%) who underwent postoperative radiotherapy. Major leakages (fistula enlargement to 9 to 15 mm) were observed in 8 patients (18.2%). These latter patients required more than 3 interventions, including soft tissue augmentation, oversewing, and the placement of a purse-string suture. In 13.6% of the irradiated patients, the fistula was enlarged to a diameter of more than 15 mm. In the 16 patients who did not receive radiotherapy, minor leakages were seen in 3 patients (18.75%) and recurrent periprosthetic leakages were seen in 3 patients (18.75%) whose fistula was enlarged to a diameter between 9 and 15 mm. Severe fistula enlargement (greater than 15 mm) was observed in 1 patient (6.25%; Table 8).

Both a univariate analysis and a multivariate analysis of the influence of supraesophageal reflux and radiotherapy showed that unlike radiotherapy, reflux can promote the occurrence of fistula enlargement (Table 9).

DISCUSSION

The placement of a speech valve through a fistula is the gold standard in prosthetic voice rehabilitation following total laryngectomy. The insertion of a voice prosthesis is a simple surgical procedure that is associated with only a moderate increase in operating time, a low rate of complications, an excellent speech rehabilitation outcome, and a success rate of up to 90%.[1,2] It is true that voice prostheses require intensive follow-up care and must be replaced regularly. However, this disadvantage is offset by the fact that voice prostheses rapidly enable patients to use speech again and thus aid in social reintegration.

Periprosthetic leakage in association with moderate fistula enlargement is the most common relevant complication reported by patients who receive a voice prosthesis after laryngectomy. In the literature, the incidence of this complication ranges from 6% to 39%.[2-4,7] In our patient population, periprosthetic leakage of varying severity was seen in 48% of the cases. Risk factors identified in the literature include hypertension, diabetes mellitus, postoperative radiotherapy, trauma during prosthesis replacement procedures, and pathological gastroesophageal reflux.[3,4,7-9]

In our patient population, we did not find a direct relationship between the occurrence of fistula enlargement and postoperative radiotherapy. The RR was 0.98 for mild enlargement and 1.195 for severe enlargement. Similar results for patients who underwent postoperative radiotherapy were reported by other research groups.[2-4,13] Three of our patients with marked fistula enlargement, however, showed a stenosis in the region of the neopharynx. The pres-

TABLE 8. OCCURRENCE OF FISTULA PROBLEMS AND POSTOPERATIVE RADIOTHERAPY

	Irradiated Patients (n = 44)	*Nonirradiated Patients (n = 16)*	*p*	*Relative Risk*	*95% Confidence Interval*
No leakage or <3 interventions (n = 31)	22 (50.0%)	9 (56.25%)			
Leakage (>3 interventions); fistula diameter of <9 mm; atrophy (n = 11)	8 (18.2%)	3 (18.75%)	NS	0.98	0.6641 to 1.476
Fistula enlargement; fistula diameter of 9-15 mm (n = 11)	8 (18.2%)	3 (18.75%)	NS	0.98	0.6641 to 1.476
Fistula enlargement; fistula diameter of >15 mm (n = 7)	6 (13.6%)	1 (6.25%)	NS	1.195	0.8453 to 1.691

Relative risk was determined by comparing irradiated and nonirradiated patients with use of 2 × 2 contingency tables and Fisher's exact test.

TABLE 9. UNIVARIATE AND MULTIVARIATE ANALYSIS OF INFLUENCE OF SUPRAESOPHAGEAL REFLUX AND RADIOTHERAPY ON DEVELOPMENT OF FISTULA ENLARGEMENT

Variable	*No. of Patients*	*p (Univariate)*	*p (Multivariate)*
Supraesophageal reflux (No. of events)		0.045	0.07
Enlargement	56 (93%)		
No enlargement	4 (7%)		
Supraesophageal reflux (reflux area index score)		0.022	0.019
Enlargement	52 (87%)		
No enlargement	8 (13%)		
Supraesophageal reflux (DeMeester score)		0.02	0.018
Enlargement	42 (70%)		
No enlargement	18 (30%)		
Radiotherapy		0.505	0.67
Enlargement	44 (73%)		
No enlargement	16 (27%)		

ence of stenosis in this region is associated with a marked flow rate increase during swallowing. The resulting pressure peaks can cause periprosthetic leakage.[2] Patients with supraesophageal reflux did not show increased biofilm formation.

Laryngopharyngeal reflux is a disease that has become a major focus of attention in the field of otolaryngology. The diagnostic gold standard is 24-hour dual-probe pH monitoring. Treatment is usually medical, with proton pump inhibitors, and can include laparoscopic fundoplication in severe cases or in cases refractory to therapy with proton pump inhibitors.[14-16]

In the present study, there was no correlation between diabetes mellitus, hypertension, or postoperative radiotherapy and an increased risk of fistula enlargement with periprosthetic leakage. The situation is different for supraesophageal reflux. Our study confirmed earlier results reported by our working group and other research groups, according to which patients with laryngeal carcinoma show an increased incidence of pathological reflux.[17-20] Smoking and alcohol use have been identified as major causes.[21] In addition, typical anatomic changes after laryngectomy, laryngeal nerve resection, and removal of the larynx lead to disturbances of esophageal motility and antireflux barriers. The tone of the upper esophageal sphincter is usually decreased, and the contractility of the proximal esophagus is reduced.[6]

In the literature, wound healing problems in the upper aerodigestive tract and an increased pharyngocutaneous fistula rate have been repeatedly reported in patients with reflux disease.[22,23] To our knowledge, however, a relationship between periprosthetic leakage or fistula enlargement and reflux has only been demonstrated by our working group.[8,9] In contrast, evidence of a tendency toward increased granulation tissue formation, increased tracheoesophageal puncture failure, and increased cricopharyngeal stenosis or spasm has been described elsewhere in association with supraesophageal reflux.[6]

Damaging effects of gastric fluid in the region of the esophagus have been widely documented in the literature and can range from esophageal erosion to adenocarcinoma. Whereas the morphology of the esophageal mucosa provides a natural barrier to physiological reflux events, pharyngeal and tracheal mucosae are completely unprotected from acid exposure. Studies on extraesophageal and laryngopharyngeal reflux showed that a few reflux episodes are sufficient to cause massive damage.[14,17,23,24] In the literature, the threshold for damage to the pharyngeal mucosa varies from 6 to 10 reflux events per 24 hours.[11,12,20]

Damage to the mucosa can be caused by the low pH values of gastric acid, pepsin, pancreatic enzymes, and bile acid.[24,25]

Especially after postoperative radiotherapy, tumor patients show reduced esophageal clearance and have an impaired bicarbonate buffering system in the presence of salivary gland damage induced by radiotherapy.[26] For this reason, even small amounts of acid can cause severe damage as a result of longer exposure times. The damaging effects of gastric fluid on the mucosa of the upper respiratory tract were demonstrated in animal studies, in which laryngeal granulomas[24] and subglottic stenosis[25] were created.

It is unlikely that acid exposure leads to severe fistula enlargement and subsequent atrophy of the membranous wall of the trachea and thus to periprosthetic leakage on the esophageal side of the fistula. This would require long and frequent exposures, which were not seen in our patient population despite clearly pathological values.

By contrast, the mucosa on the tracheal side of the fistula may be exposed to gastric fluid passing through the tracheoesophageal fistula. The respiratory epithelium in the region of the trachea does not possess protective mechanisms against gastric acid exposure. As a result, the mucosa can be damaged by both a low pH value and proteolytic enzymes such as pepsin and trypsin, which are components of gastric juice.[25] The effects of these enzymes last for up to 1 hour after exposure. In addition, it is possible that reflux-induced damage is increased by mi-

cro-injuries to the mucosa of the tracheoesophageal fistula during prosthesis replacement procedures.

A comparison of our patient groups in terms of the frequency and severity of reflux episodes shows that patients with severe supraesophageal reflux disease experienced significantly more problems in the region of the fistula, such as granulation tissue formation, periprosthetic leakage, and severe fistula enlargement. This is reflected not only in the results for the RAI, which is currently regarded as the most sensitive parameter for detecting esophageal and extraesophageal reflux episodes, but also in the absolute numbers of reflux events and the DeMeester scores.[10,11] In addition, all patients with marked fistula enlargement were found to have pathological reflux.

Our study also demonstrated that the life span of voice prostheses was reduced in patients with reflux. This effect, however, can at least partially be explained by the enlargement of the speech fistula that is often seen in these patients and that requires removal or replacement of the prosthesis for the management of leakage. Periprosthetic leakages should be managed by use of a specific algorithm. Patients with periprosthetic leakage and a fistula diameter of less than 12 mm should be treated with oral antireflux medications and a silicone washer[7] or soft tissue augmentation.[4] In patients with larger fistula diameters, it is usually impossible to leave the voice prosthesis in situ. In these cases, we recommend the removal of the prosthesis, the insertion of a cuffed tracheal cannula to prevent aspiration, and the placement of a nasogastric feeding tube or a percutaneous endoscopic gastrostomy tube to maintain nutrition. Treatment should then consist of high doses of antireflux medications and injections of granulocyte colony-stimulating factor in order to encourage shrinkage of the fistula. If this treatment fails, the fistula must be closed with a pedicled or free flap. The speech fistula can be recreated after 3 to 6 months.[8]

The purpose of this study was to investigate the relationship between the severity of reflux and the occurrence of tracheoesophageal fistula complications following laryngectomy. We studied objective reflux parameters using 24-hour dual-probe pH monitoring and found a clear relationship between the severity of reflux and the extent and frequency of fistula complications. A study population of 60 patients and the objective assessment of reflux episodes using dual-probe pH monitoring allowed us to draw concrete conclusions about the role of reflux in the development of fistula complications. Against this background, a prospective study should investigate whether patients with fistula problems and reflux benefit from treatment with antireflux medications.

In our opinion, the results that we obtained for patients with severe fistula problems justify prophylactic antireflux treatment with proton pump inhibitors, which is also recommended by Pattani et al[6] for patients with tracheoesophageal puncture failure.

CONCLUSIONS

This study demonstrated beyond doubt that there is a direct relationship between the severity of reflux and the occurrence of fistula problems, especially periprosthetic leakage. For this reason, prophylactic treatment with antireflux medications appears to be justified in all laryngectomized patients with recurrent or severe fistula complications.

In addition, we recommend that patients earmarked for laryngectomy undergo preoperative 24-hour pH monitoring. Patients at risk can thus be identified and can receive antireflux treatment at an early stage.

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