Impact of fundoplication for gastroesophageal reflux in the outcome of benign tracheal stenosis

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ABSTRACT

Objective: This study focuses on the impact of antireflux surgery in the outcome of tracheal stenosis.

Methods: We performed a retrospective study including patients with benign tracheal stenosis who underwent esophageal manometry and dual-probe 24-hour ambulatory esophageal pH study. Patients with an abnormal pH study were managed with laparoscopic modified Nissen fundoplication or medically (omeprazole 80 mg/d, orally). Patients with normal pH study results were observed. After a 24-month follow-up, the outcome was considered satisfactory if tracheal stenosis could be managed by resection and there was no need for further dilatation or definitive decannulation. The management groups were compared using propensity score matching.

Results: A total of 175 patients were included. Abnormal pH study results were found in 74 patients (42.3%), and 12.6% of patients had typical gastroesophageal reflux symptoms. Follow-up was completed in 124 patients (20 had fundoplication, 32 received omeprazole, and 72 were observed). After propensity score matching, the outcome of tracheal stenosis in the fundoplication group was similar to that of the observation group (odds ratio, 1; $P = .99$) and better than that of the omeprazole group (odds ratio, 5.31; $P = .03$). The observation (no gastroesophageal reflux) group had a better outcome of stenosis than those treated with omeprazole (odds ratio, 3.54; $P = .02$).

Conclusions: The outcome of the airway stenosis was superior after laparoscopic fundoplication compared with medical treatment with omeprazole and was similar to the outcome of patients without gastroesophageal reflux. A prospective randomized trial is warranted. (J Thorac Cardiovasc Surg 2019;158:1698-706)

Frequency of the outcomes of tracheal stenosis according to the management strategy.

Central Message

Detection of pathologic GER and its treatment by fundoplication yield a better outcome of benign tracheal stenosis compared with medical treatment with high-dose omeprazole.

Perspective

The positive impact of antireflux surgery in the outcome of benign tracheal stenosis in patients with pathologic GER may change the future management strategy of airway stenosis.

See Commentaries on pages 1707 and 1708.

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Postintubation airway stenosis is a complex problem that often requires multiple interventions for treatment and poses a negative impact on the patient's quality of life.¹ The reported incidence of tracheal stenosis after tracheostomy and laryngotracheal intubation varies from 0.6% to 21%.² Gastroesophageal reflux (GER) is associated with a wide spectrum of respiratory diseases, including pulmonary fibrosis, bronchiectasis, and asthma.³⁻⁵ The association between laryngopharyngeal reflux and subglottic stenosis has been described, particularly in idiopathic tracheal stenosis, but its correlation remains controversial.⁶

The high number of patients referred to our center with complex airway stenosis, such as subglottic, laryngotracheal, long-segment, postresection recurrences of tracheal stenosis, and persistent inflammation at the stenosis site, led us to investigate the involvement of other potential

Abbreviations and Acronyms

BMI	= body mass index
GER	= gastroesophageal reflux
GERD	= gastroesophageal reflux disease
LES	= lower esophageal sphincter
PSM	= propensity score matching
UES	= upper esophageal sphincter

contributing factors such as GER. The detection of GER relies on the usual clinical manifestations such as heartburn and acid regurgitation, which are often absent or undetectable in patients with respiratory disease unless a specific diagnostic workup is carried out using esophageal motility and ambulatory 24-hour pH studies. On the basis of the clinical findings, outcome of tracheal stenosis, and results of the esophageal function, we hypothesized that GER can potentially influence the outcome of benign tracheal stenosis.

The present study is focused on the impact of antireflux surgery in the outcome of benign tracheal stenosis in patients with pathologic acid reflux.

PATIENTS AND METHODS

The study was approved by the hospital's ethics committee (Cappesq 1.195.397;1.684.969). The study design was retrospective and included adult patients with benign airway stenosis seen at the Division of Thoracic Surgery Trachea and Airway clinic between August 2011 and May 2017. Patients signed the generic informed consent of the hospital for diagnostic and surgical procedures. Data collection was extracted from the electronic patient records by diagnosis and was blinded for the patient's name. Data collection included the demographics and presence of typical GER symptoms, defined as the association of heartburn and acid regurgitation occurring at least once per week. Any degree of dysphagia regardless of aspiration and presence of other respiratory symptoms, such as dyspnea, cough, and stridor, were recorded. Previous treatments of the stenosis (tracheostomy, dilatation, and previous tracheal resection) were also recorded. Location and length of the airway stenosis were obtained by airway endoscopy and computed tomography scan with reconstructions. The criteria for performing the esophageal function studies included one of the following: high tracheal stenosis (proximal end within 4 cm below the vocal cords); blind-end stenosis (Myer-Cotton grade 4)⁷; recurrent tracheal stenosis refractory to dilatation (≥ 3 dilatation sessions); and recurrent stenosis within 5 years after tracheal resection. Patients with previous antireflux surgery, esophagectomy, gastrectomy, and incomplete follow-up were excluded. A 2-year follow-up was considered as complete. All patients who did not complete follow-up were excluded.

Esophageal motility and 24-hour pH studies were performed in the same esophageal motility laboratory by 1 investigator (A.N.). Manometry used an 8-channel, water-perfused catheter connected to a low-compliance pneumohydraulic pump (Multiplex II, Alacer Biomedica, Sao Paulo, Brazil). The lower esophageal sphincter (LES) and upper esophageal sphincter (UES) position and pressure, esophageal body motility pattern, and pressures were recorded. Normal values used were the standardized values of the laboratory.⁸ The 24-hour ambulatory esophageal pH monitoring consisted of a dual-channel antimony electrode catheter and a logger (AL-3, Alacer Biomedica). The distal tip of the probe was positioned 5 cm above the upper end of the LES located by manometry. The proximal electrode was located between 15 and 18 cm above the distal electrode. Antacid and prokinetic medications were suspended 7 days before esophageal function testing.

The pH study used the pH less than 4 cutoff for acid reflux, and the results used standard reference values.⁹ Abnormal (pathologic) reflux was considered when the DeMeester score was greater than 14.7. Data were retrieved from the medical records of the patients and collected by 2 investigators blinded for patient identity. Data collected were plotted on Excel (Microsoft Inc, Redmond, Wash) and transferred later to a RedCap platform (RedCap version 7. 6.10, Vanderbilt University, Nashville, Tenn).

Study Groups

- **Fundoplication.** Patients with pathologic reflux included in the 24-hour ambulatory esophageal pH study were considered for laparoscopic fundoplication in multidisciplinary rounds. Main criteria included the presence of reflux complications (eg, severe erosive esophagitis, Barrett's), typical GER symptoms, clinical treatment failure, and patient consent. Additional criteria included DeMeester score greater than 30, the absence of severe comorbidities (type 1 diabetes, severe cardiovascular condition, kidney failure, asthma, or chronic obstructive pulmonary disease), and body mass index [BMI] greater than 30 kg/m².
- **Omeprazole.** Patients with pathologic GER as detected by 24-hour ambulatory esophageal pH study who did not fulfill the criteria for fundoplication received omeprazole (40 mg twice per day orally), regardless of the presence of typical upper gastrointestinal symptoms.
- **Observation (no GER).** Patients with a normal 24-hour esophageal pH study were followed during the study period.

Patients treated with omeprazole received gratuitous medication provided by the hospital's dispensary. Adherence to treatment was checked bimonthly during visits to the outpatient clinic. A laparoscopic modified Nissen fundoplication was performed under general anesthetic using a 4-port technique. A 360° tension-free 1.5- to 2-cm wrap of the gastric fundus was constructed around the distal esophagus after transhiatal mobilization to allow approximately 3 cm of intra-abdominal esophagus and division of the short gastric vessels.^{10,11} Repeat esophageal motility and dual-probe 24-hour pH study were carried out 6 months after the fundoplication.

Definition of Outcomes

The data collected for sample characterization included age, sex, BMI, symptoms (dyspnea, dysphonia, heartburn, acid regurgitation, phlegm, dysphagia, stridor, globus), presence of lower esophageal or body sphincter hypotonia, presence of supraesophageal reflux, DeMeester score, presence of tracheostomy, recurrence of previous treatment of the stenosis, and other treatment used for the tracheal stenosis. Favorable outcome of the tracheal stenosis was considered when at completion of the 2-year follow-up the patient achieved 1 of the following conditions: stability of the stenosis not requiring further dilatation or allowing for definitive decannulation using standardized criteria¹² or tracheal resection was performed successfully according to endoscopic and radiology assessment. Unfavorable outcome was considered when none of those outcomes were achieved after 2 years of follow-up.

Statistical Analysis

Descriptive analysis for numeric data was represented as mean and standard deviation. Categorical data are represented as frequencies and percentages. For comparison of several proportions and variance among the 3 groups, we used the chi-square test and analysis of variance. For analysis among the treatment groups, the comparison was performed in pairs (fundoplication $\times$ omeprazole, fundoplication $\times$ observation, omeprazole $\times$ observation). A Fisher test was performed for categorical variables. For continuous variables, the statistical difference between the groups was calculated using Mann-Whitney and Brunner-Munzel *t* tests. DeMeester score and BMI were confounding factors in the analysis causing selection bias. Propensity score matching (PSM) was then performed to mitigate the effects of sample inequality and used in the comparison between the patient groups. Matching between the groups was performed

using the PSM by the “closest neighbors” algorithm.¹³ The variables used in the pairing were previously selected by the Levene and Kruskal–Wallis tests for the continuous variables and by the chi-square test for the categorical variables, considering the 3 groups (fundoplication, observation, and omeprazole). The variables that showed statistical significance in this first step were used within the STEP-AIC forward method in each pairing. The variables used in PSM were chosen by the Akaike criteria¹⁴ and were DeMeester score, age, and BMI, because they had significance and were present in all the pairings. Pairing quality was ascertained using distance density graphs. Group comparison was done by logistic regression using the stepwise-forward method. All PSM analyses used SPSS 21 for Windows (SPSS Inc, Chicago, Ill) and R Core team software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 175 patients were included (106 male and 69 female; median age, 38.5 years; range, 13–85 years). A total of 162 patients (92.5%) had a history of orotracheal intubation with a median duration of 17.1 days. Other causes in the remaining patients were idiopathic (9), postinfectious stenosis (3), and Wegener’s granulomatosis (1). The location of the stenosis was subglottic in 94 (53.7%), tracheal in 61 (34.8%), and laryngotracheal in 20 (11.4%). The median extension of the stenosis was 2.6 cm. Tracheal restenosis accounted for 42 (27.4%) of all patients. There were 145 patients (82.8%) with a tracheostomy; 75 (42.8%) of those had a previous resection (42 tracheal resections, 23 laryngofissures, 10 subglottic resections). Dilatation was performed in 48 patients (27.4%) (1.1 dilatations/patient). Stenting was required to maintain airway patency in 160 patients (69.7%). A silicone T-tube was used in 122 patients (69.7%), and 88 were placed with the vertical limb below the vocal cords. A Dumon stent was used in 38 patients (21.7%). BMI of the cohort was $26.9 \pm 4.7 \text{ kg/m}^2$, and there was no significant difference between normal and an abnormal pH study ($27 \pm 5.1 \text{ kg/m}^2$, $26.6 \pm 4 \text{ kg/m}^2$, respectively; $P = .91$) or between normal and abnormal esophageal manometry findings ($P = .59$).

An abnormal esophageal motility was found in 63 of 171 manometries (37.3%), and hypotonic LES was the predominant finding (67.1%). Esophageal body motor abnormality was found in 28 patients (44.4%), 20 patients showed hypomotility, and 5 patients had hypercontractility of the distal esophagus. Other findings included nonspecific motility disorder (1), diffuse esophageal spasm (1), and hypertonic UES (1). The presence of an abnormal esophageal motility in this cohort was not affected by age or gender ($P = .504$ and $P = .435$, respectively). The presence of dysphagia was not different between normal and abnormal esophageal manometry (13.2% and 14.3%, respectively; $P = .843$).

There were 175 dual-probe 24-hour ambulatory pH studies. There were 74 patients (42.3%) with an abnormal pH study, and all had postintubation tracheal stenosis. These patients had a higher number of distal acid reflux episodes, higher orthostatic and supine acid reflux exposure, and twice as much supraesophageal reflux. Upper

gastrointestinal endoscopy was performed in 54 patients (30.6%) (20 patients with normal pH study and 34 patients with abnormal pH study). Abnormalities were found in 10 patients (18.5%): 8 patients with an abnormal pH study and 2 patients with a normal pH study. Esophagitis was found in 8 patients, Barrett’s esophagus was found in 1 patient, and hiatus hernia was found in 1 patient.

Dominant symptoms were dyspnea (89.7%), dysphonia (34.3%), heartburn (31.6%), and acid regurgitation (27.6%). Patients with an abnormal pH study had a higher incidence of heartburn (67.3%) and acid regurgitation (56.3%) compared with those with a normal pH study (32.7%, $P = .0001$; 34.8%, $P = .024$, respectively). A combination of heartburn-acid regurgitation occurred in 21.1% of the patients and was related to a higher chance of an abnormal pH study (odds ratio, 2.42; 95% confidence interval, 0.156–5.090; $P = .017$). Dyspnea, dysphonia, phlegm, stridor, and globus were not different between patients with normal and abnormal pH study results.

Among the 175 patients, 51 were excluded because they had not completed the 2-year follow-up, leaving 124 for analysis (52 with an abnormal pH study and 72 with a normal pH study) (Figure 1). The percentage of patients with a previous tracheal resection was similar in both the fundoplication and omeprazole groups, and smaller in the observation (no GER) group (20%, 17.6%, and 9.7%, respectively). The treatment for tracheal stenosis was categorized into tracheal resection, dilatation, and stenting with a Dumon stent or a silicone T-tube (Table 1).

The percentage of patients with a favorable outcome of stenosis in the fundoplication group (65%) was similar to that in the observation group (61%) and higher than in

FIGURE 1. Flowchart showing the distribution of the patients in the study.

TABLE 1. Patient demographics showing frequencies distributed by groups

Patient demographics (n = 124)	Fundoplication (n = 20)	Omeprazole (n = 32)	Observation (no GER) (n = 72)	P*
Age	33.5 ± 12.2	47.7 ± 15.4	43.9 ± 18.6	.012
BMI	23.7 ± 2.7	27.1 ± 3.9	25.9 ± 4.9	.028
DeMeester score	47.7 ± 17.7	30.5 ± 22.9	6.6 ± 4.3	.001
Male (%)	11 (55)	23 (71.8)	45 (62.5)	.643
Female (%)	9 (45)	9 (28.1)	27 (37.5)	.354
Heartburn (%)	13 (65)	14 (43.7)	15 (20.8)	.001
Acid regurgitation (%)	11 (55)	11 (34.3)	14 (19.4)	.006
Hypotonic LES (%)	10 (50)	6 (18.7)	18 (25)	.032
Tracheostomy (%)	16 (80)	30 (93.7)	56 (77.7)	.487
Previous tracheal resection (%)	6 (30)	6 (18.7)	7 (9.7)	.073
Tracheal resection (%)	4 (20)	6 (18.7)	21 (29.1)	.407
Tracheal stenosis dilatation (%)	5 (25)	4 (12.5)	10 (13.8)	.398
Silicone T-tube stent (%)	10 (50)	21 (65.6)	32 (44.4)	.271
Dumon silicone stent (%)	1 (5)	3 (9.3)	9 (12.5)	.779
Favorable outcome (%)	13 (65)	12 (37.5)	44 (61.1)	.028

GER, Gastroesophageal reflux; BMI, body mass index; LES, lower esophageal sphincter. *Analysis of variance; chi-square. Patients undergoing fundoplication were younger and had slightly lower BMI, higher pH study scores (DeMeester), more typical reflux symptoms (heartburn and regurgitation), and a higher incidence of hypotonic LES. A higher percentage of these patients achieved a favorable outcome of the tracheal stenosis at the end of follow-up.

the omeprazole group (37%) (Table 1). Frequency of a favorable outcome of the tracheal stenosis was higher in the fundoplication group compared with omeprazole ($P = .043$) and in the observation (no GER) group compared with omeprazole ($P = .034$). The PSM was performed, and the 3 groups were compared in pairs (Tables 2 and 3). After logistic regression analyses, the results were as follows:

- Fundoplication versus omeprazole: A total of 18 subjects were paired in each group. Patients who received fundoplication had a better chance of a favorable outcome than patients treated with omeprazole ($P = .03$). The pairing quality using the distance-density graphs before and after PSM and the results of the analysis are shown in Figure 2. The covariable hypotonic LES was maintained in the model for the purpose of quality adjustment.
- Omeprazole versus observation: A total of 29 subjects were paired in each group. Patients in the observation (no GER) group had a better chance of achieving a favorable outcome compared with the patients treated with omeprazole ($P = .02$). The covariable BMI was maintained in the model for the purpose of quality adjustment (Figure 3).
- Fundoplication versus observation (no GER): A total of 18 subjects were paired in each group. No significant difference in favorable outcome was found between the fundoplication and observation (no GER) groups ($P = .99$). The covariable hypotonic LES was kept in the model for the purpose of quality adjustment (Figure 4). Two patients were kept on omeprazole after fundoplication.

DISCUSSION

This retrospective study using PSM showed that patients with benign tracheal stenosis in a setting of an abnormal esophageal acid exposure experienced a better outcome of the stenosis after antireflux laparoscopic fundoplication.

Airway-related problems in patients with GER carry an inflammatory component that is often associated with the presence of neutrophilic, neuroendocrine, inflammatory cells, and cytokines, thus causing airway inflammation and increased local oxidative stress.¹⁵ The potential role of GER in our patient population with benign tracheal stenosis was considered after the observation of persistent inflammation found at the stenosis site in young patients with postintubation tracheal stenosis submitted to stenting and in the late recurrences after tracheal resection.¹⁶

The acronym GER was used in this study instead of gastroesophageal reflux disease (GERD) because most subjects in the cohort did not fulfill the criteria for GERD, that is, the presence of typical symptoms regardless of an injured esophageal mucosa.

This cohort has a predominance of postintubation tracheal stenosis, high airway stenosis (subglottic or laryngotracheal), restenosis, and previous resection failures. The high number of silicone T-tube stents derives from most patients already having a tracheostomy in place upon referral to our center. Nevertheless, stenting by means of a T-tube was used mostly as a bridge to definitive treatment.

For the purpose of the study, the typical symptoms were defined as the combination of heartburn and acid

TABLE 2. Patient demographics showing frequencies and outcomes distributed by groups after propensity score matching was applied: Group comparisons in pairs

Variables	Fundoplication vs omeprazole			Fundoplication vs observation (no GER)			Observation (no GER) vs omeprazole		
	Fundoplication (N = 18)	Omeprazole (N = 18)	P*	Fundoplication (N = 18)	Observation (N = 18)	P*	Observation (N = 29)	Omeprazole (N = 29)	P*
Age	33.6 ± 12.9	45.2 ± 13.4	.012	33.6 ± 12.9	43.3 ± 21.1	.223	41.5 ± 17.0	45.2 ± 15.4	.316
BMI	23.7 ± 2.9	27 ± 3.8	.007	23.7 ± 2.9	24.3 ± 5.2	.798	25.9 ± 5.1	27.3 ± 4	.129
DeMeester score	Before 47.7 ± 17.7 After 6.8 ± 13	26.8 ± 12	<.001	Before 47.7 ± 17.7 After 6.8 ± 13	9.3 ± 4.3	<.001	2.6 ± 1.6	31.48 ± 24.4	<.001
Gender (%)									
Male	5 (27.7)	3 (16.6)	.691	5 (27.7)	5 (27.7)	1	11 (37.9)	8 (27.5)	.576
Female	13 (72.2)	15 (83.3)		13 (72.2)	13 (72.2)		18 (62.0)	21 (72.4)	
Heartburn (%)	12 (66.6)	9 (50)	.5	12 (66.6)	0 (0)	<.001	5 (17.2)	13 (44.8)	.045
Acid regurgitation (%)	10 (55.5)	7 (38.8)	.505	10 (55.5)	2 (11.1)	.012	4 (13.7)	11 (37.9)	.07
Hypotonic LES (%)	9 (50)	2 (11.1)	.027	9 (50)	7 (38.8)	.738	3 (10.3)	6 (20.6)	.47
Tracheostomy (%)	15 (83.3)	17 (94.4)	.603	15 (83.3)	13 (72.2)	.691	24 (82.7)	25 (86.2)	1
Previous tracheal resection (%)	5 (27.7)	2 (11.1)	.402	5 (27.7)	2 (11.1)	.402	2 (6.9)	5 (17.2)	.423
Recurrence (%)	5 (27.7)	3 (16.6)	.691	5 (27.7)	5 (27.7)	1	7 (24.1)	6 (20.6)	1
Treatment (%)									
Tracheal resection	4 (22.2)	4 (22.2)	.31	4 (22.2)	4 (22.2)	1	5 (17.2)	6 (20.6)	.655
Tracheal dilatation	4 (22.2)	1 (5.6)		4 (22.2)	1 (5.5)		5 (17.2)	3 (10.3)	
T-tube silicone stent	9 (50)	13 (72.2)		9 (50)	10 (55.5)		15 (51.7)	18 (62)	
Dumon silicone stent	1 (5.5)	0 (0)		1 (5.5)	0 (0)		4 (13.7)	2 (6.9)	
Favorable outcome (%)	12 (66.6)	5 (27.7)	.043	12 (66.6)	10 (55.5)	.733	18 (62)	9 (31)	.034

GER, Gastroesophageal reflux; BMI, body mass index; LES, lower esophageal sphincter. *Fisher, Mann–Whitney. The comparison among the 3 groups in pairs (Fisher, Mann–Whitney) showed that more patients undergoing fundoplication were able to achieve a favorable outcome of the tracheal stenosis compared with those treated medically (omeprazole) and had a similar frequency compared with patients in the observation (no GER) group. Conversely, only half the patients treated with omeprazole achieved a favorable outcome compared with those in the observation (no GER) group.

regurgitation found in 21% of the cohort and in only 12% patients with tracheal stenosis and an abnormal pH study. Such findings approximate the prevalence values for

heartburn in healthy subjects previously reported in Brazil (11.9%)¹⁷ and heartburn or acid regurgitation in subjects in the United States (19.8%).¹⁸

TABLE 3. Standardized differences of the variables studied before and after propensity score matching was applied to the groups

Variables	Before PSM			After PSM		
	Fundoplication vs omeprazole	Fundoplication vs observation (no GER)	Observation (no GER) vs omeprazole	Fundoplication vs omeprazole	Fundoplication vs observation (no GER)	Observation (no GER) vs Omeprazole
Age	0.834	0.674	0.062	0.703	0.216	0.245
DeMeester score	0.832	3.406	1.43	0.554	3.229	1.668
BMI	0.992	0.57	0.248	0.486	0.269	0.287
Gender	0.004	0.26	0.265	0.237	0.352	0.222
Heartburn	0.451	1.067	0.55	0.343	1.649	0.625
Acid regurgitation	0.359	0.832	0.443	0.339	1.292	0.573
Hypotonic LES	0.644	0.47	0.164	0.756	0.343	0.289
Tracheostomy	0.08	0.124	0.204	0	0.161	0.095
Previous tracheal resection	0.254	0.492	0.238	0.27	0.625	0.322
Stenosis recurrence	0.166	0.002	0.164	0.129	0	0.083
Favorable outcome	0.763	0.139	0.608	0.579	0	0.655

PSM, Propensity score matching; GER, gastroesophageal reflux; BMI, body mass index; LES, lower esophageal sphincter.

FIGURE 2. Comparison of outcomes between patients receiving fundoplication and patients receiving omeprazole. The pairing quality is shown by the distance-density graphs before and after PSM. Results of the regression analysis demonstrated that fundoplication resulted in a higher chance of resolution of the tracheal stenosis. The covariable hypotonic LES was used for quality adjustment. *LES*, Lower esophageal sphincter.

We elected to use a 24-hour ambulatory dual-probe esophageal pH study for the detection of GER regardless of the presence of typical digestive symptoms and was based on the characteristics and complexity of the stenosis. This strategy is used in other respiratory conditions, such as in lung transplant candidates in whom GER is associated with graft dysfunction, justifying a practice of universal esophageal manometry and pH testing in this population.¹⁹ The authors acknowledge that this approach may have limited data acquisition to ascending acid GER and overlooks the descending laryngopharyngeal reflux. In the present study, 37% of the patients undergoing esophageal manometry had esophageal motility abnormalities represented mostly by hypotonic LES followed by distal esophageal hypocontractility. The incidence of dysphagia was less than 15%, and it was not different between patients with normal and abnormal esophageal manometry findings.

Unlike other airway or lung diseases, such as asthma,^{4,5} pulmonary fibrosis,³ bronchiolitis obliterans,^{19,20} and airway hyperresponsiveness, the few studies²¹⁻²³ on the correlation between airway stenosis and GER are focused on idiopathic subglottic airway stenosis where the presence of gastric juice yields to tissue remodeling through the stimulation of the differentiation of fibroblasts into myofibroblasts.²⁴

As far as postintubation tracheal stenosis is concerned, the treatment of reflux and its impact on the outcome of the stenosis have been scarcely reported. Bain and colleagues²⁵ described the first case of successful improvement of a laryngotracheal stenosis after surgical treatment for

GERD. Experimentally, both tracheal injury and stenosis are aggravated after exposure to the acid contents of the stomach.²⁶ Up to 78% of the patients with upper airway stenosis show an abnormal 24-hour pH study,²⁷ and this high prevalence of abnormal acid reflux occurs in the absence of typical digestive symptoms. A higher incidence of pharyngeal acid reflux events has been reported, and the treatment of GER improved the results of the treatment of the airway stenosis.²⁸ Our study showed a high incidence of abnormal pH studies (42%) with a predominance of supine and supraesophageal reflux, similar to previous reports in other respiratory diseases.^{3,4,20} Laryngotracheal stenosis is associated with an abnormal pH study in more than half the patients,²² whereas the laryngeal acid exposure occurs in 86%.⁶ Another study on tracheal stenosis found GERD in 47% of the patients, although, as opposed to our cohort, only 18% of the patients had postintubation stenosis.²⁹

Clinical data on the effects of laryngotracheal stenosis on upper airway aerodynamics showed an increased resistance and a decreased airflow that are not compensated by mouth breathing.³⁰ Therefore, thoracoabdominal pressure gradients may contribute to the pathogenesis of GER by overcoming the antireflux barrier function. A dog model of airway obstruction submitted to esophageal motility and a pH study demonstrated that the severity of reflux correlated with negative inspiratory pressure changes.³¹ The role of thoracoabdominal pressure gradient assessed in lung transplant candidates found GERD in 30% of the patients with a thoracoabdominal pressure gradient less than 0 mm Hg.

FIGURE 3. Comparison of outcomes between patients receiving medical treatment of reflux with omeprazole and patients without pathologic reflux. The pairing quality is shown by the distance-density graphs before and after PSM. Results of the regression analysis demonstrated that patients receiving treatment of reflux with omeprazole had a lower chance of resolution of the tracheal stenosis. The covariable BMI was used for quality adjustment. *BMI*, Body mass index.

Higher adjusted thoracoabdominal pressure gradient increased the likelihood of pathological reflux in these patients, even in the absence of a hiatus hernia or hypotonic LES.³²

Despite the pathophysiologic differences between pulmonary and central airway disease, variations in thoracoabdominal and transpulmonary pressures can be transposed to the airway dynamics when flows are altered in tracheal

FIGURE 4. Comparison of outcomes between patients receiving fundoplication for the treatment of reflux and patients without pathologic reflux who were observed only. The pairing quality is shown by the distance-density graphs before and after PSM. Results of the regression analysis demonstrated that patients receiving fundoplication had a similar chance of resolution of the tracheal stenosis compared with the observation (no GER) group. The covariable hypotonic LES was used for quality adjustment. *LES*, Lower esophageal sphincter.

stenosis. However, the high number of tracheostomies in our patient cohort makes this mechanism less likely to occur if one considers that the presence of an adult-size tracheostomy cannula can bypass the stenosis and reduce the local resistance to airflow during spontaneous breathing.

Another plausible explanation for the effects of acid reflux in the outcome of tracheal stenosis is the change in the local microbiome. This may be particularly important in patients using silicone stents because the stent's biofilm can change its microbiome depending on local conditions (ie, local pH, humidity, and temperature). The exposure of the stent to aerodigestive secretions creates a microbial challenge that can harm the tracheal wall at the stenosis site.³³ This enhanced and persistent local tissue aggression can potentially increase the extent and severity of the stenosis, thus delaying or impairing the definitive treatment.³⁴

Since the first report of antireflux surgery in the treatment of tracheal stenosis,²⁵ there were no further attempts to perform this intervention for this intent. Our study demonstrated that patients with pathologic acid reflux who underwent fundoplication had a similar outcome of the stenosis compared with subjects without pathologic reflux. Fundoplication was also associated with a better chance of an improved outcome of the tracheal stenosis compared with continuous treatment with high-dose omeprazole. Patients treated with omeprazole had a worse chance of a favorable outcome of the tracheal stenosis than patients without pathologic acid reflux or fundoplication. Omeprazole is effective in reducing the acid contents of the refluxate; however, it does not prevent supraesophageal reflux and microaspiration of gastric juice enzymes such as pepsin and other harmful components of the refluxate that can affect the tracheal stenosis. An analogous situation is described in idiopathic pulmonary fibrosis, where GER control by fundoplication reduces exacerbation of the disease and slows the decline in pulmonary function.³⁵

We acknowledge that this study is not sufficient to define whether all patients with a tracheal stenosis and abnormal GER should undergo fundoplication. However, the results paved the ground for new studies in this intriguing area of investigation.

Study Limitations

The present study has several limitations. Its retrospective design does not allow discernment of whether or when GER was present before the onset of tracheal disease in these patients. The nonrandomized patient selection yielded to the allocation of patients with more severe reflux to the fundoplication group. The worse outcome of tracheal stenosis in the omeprazole group reinforces the idea that GER itself is harmful to the stenosis. This issue needs to be addressed in the future using pH monitoring with higher sensitivity such as the catheter-free system or the

impedance-pH monitoring to measure weakly acidic and nonacid reflux, which were unavailable for use in the present study because it was not available in our institution until recently.

CONCLUSIONS

In this cohort of patients with benign tracheal stenosis and GER, the outcome of the airway stenosis was superior after laparoscopic fundoplication when compared with medical treatment with omeprazole and was similar to the outcome of patients without GER. A prospective randomized trial is warranted.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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