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Single application of airway stents in thoracogastric-airway fistula: results and prognostic factors for its healing

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Abstract

Background: Thoracogastric-airway fistula (TGAF) post-thoracic surgery is a rare and challenging complication for esophagectomy. The aim of this study was to explore the effectiveness of airway stenting for TGAF patients and find related factors coupled with healing of fistula.

Methods: This is a retrospective study involving patients with TGAF who were treated with airway stentings. Based on different TGAF locations and sizes on chest computed tomography, covered metallic or silicon airway stents were implanted to cover orifices under interventional bronchoscopy. TGAF healing was defined as the primary outcome, and complete sealing of TGAF as the second outcome. The predictors for TGAF healing were analyzed in univariate and multivariate analysis.

Results: A total of 58 TGAF patients were included, of whom 7 received straight covered metallic stents, 5 straight silicon stents, 3 L-shaped covered metallic stents, 21 large Y-shaped covered metallic stents, 17 large Y-shaped silicon stents, and 5 with Y-shaped covered metallic stents. Healing was achieved in 20 (34.5%) patients, and complete sealing in 45 (77.6%) patients. There were no significant differences in healing rate and complete sealing rate between patients receiving metallic stents and those with silicon stents. In univariate analysis, lacking a previous history of radiotherapy or chemotherapy, nonmalignant fistulas, small fistulas, and shorter postesophagectomy duration were found associated with a higher rate of TGAF healing. Only shorter postesophagectomy duration was associated with TGAF healing in multivariate analysis.

Conclusions: Both silicon and covered metallic airway stenting are effective methods to close TGAF. A shorter postesophagectomy period may predict better TGAF healing.

The reviews of this paper are available via the supplemental material section.

Keywords: airway stenting, esophageal cancer, esophagectomy, thoracogastric-airway fistula

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Introduction

Thoracogastric-airway fistula (TGAF) after thoracic surgery is a relative rare but challenging clinical situation. Although TGAF incidence is only 0.8–1.8%, it significantly affects patients' quality of life, and is reported as a negative predictor of long-term survival.[1,2] Severe cough, refractory pneumonia, frequent aspiration to the airway and lungs, malnutrition, and life-threatening hemoptysis can lead to a rapid deterioration, which is associated with a very high mortality in TGAF patients.[3–5] Complications are significantly reduced when TGAF is healed or sealed. More importantly, quality of life is notably improved when patients resume their normal intake. However, few studies have made a thorough analysis of predictors of TGAF healing due to its rareness.

Currently available approaches to treatment of TGAF include nasojejunal feeding tube/

jejunostomy, surgical repair, esophageal stenting, and airway stenting.[1,6,7] Conservative strategies, including enteral nutrition by feeding tube, intravenous nutrition, and anti-inflammatory medications, can neither prevent the leakage of gastric contents into the airway, nor resume oral feeding.[8] Surgical treatments provide the best opportunity of full recovery; however, it is impossible, or unsuitable, for most TGAF patients due to their previous surgery and poor general condition.[3,9,10] Additionally, it is unlikely that gastric stents can be placed to cover the fistula because of significant changes in the gastric volume between contraction and relaxation.[11] Therefore, airway stenting is a preferred option for TGAF patients, especially for those with tracheal stenosis. A previous paper reported a high success rate for the airway stenting technique under fluoroscopic guidance; however, healing of TGAF and prognosis was not mentioned.[1] In addition, healing or sealing rate of TGAF in histology or under bronchoscopy has only been depicted in case reports or small series. Thus, it is imperative to analyze the effectiveness of bronchoscopic stenting for TGAF patients and to elucidate potential factors predicting better healing of TGAF.

Materials and methods

This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. Informed consent was obtained from all patients, or their representatives, before stent implantation. This study was approved by Emergency General Hospital institutional review board (IRB no. 2012.11). Written informed consent was waived by the institutional review board due to the retrospective nature of this study.

This investigation was a retrospective single-center study. The inclusion criteria were as follows: aged 18 years old or older; TGAF confirmed by clinical features, upper digestive tract radiography, chest computed tomography (CT) findings, and bronchoscopy; and TGAF treated by airway stenting.[4] Exclusion criteria were: incomplete data in medical file; and TGAF combined with esophagopleural fistula.

Pretreatment evaluation

All patients accepted the following assessments: upper digestive tract radiography; CT scan of the larynx, trachea and lungs; flexible or rigid bronchoscopy, or both; and upper gastrointestinal endoscopy. The size of the fistula's orifice in bronchoscopy was divided in two groups: small ($\leqslant$10 mm) and large ($>$10 mm).[4,10] Oral intake was prohibited. Enteral nutritional support was ascertained through a jejunostomy or feeding tubes, and parenteral nutrition was supplied as supplement. Total energy intake was ensured no less than 35 kcal/(kg day).[12] Pulmonary infection was treated with antibiotics. Karnofsky Performance Score (KPS) was applied to estimate the quality of life of TGAF patients.

Airway stenting

General anesthesia was given prior to flexible or rigid bronchoscopy. Both Dumon™ silicon stents (Novatech, La Ciotat, France) and covered metallic stents (Micro-Tech Medical Company, Nanjing, China) were placed. The largest diameter of silicon stents in China is 20 mm. Silicon stents were not chosen when the insert of rigid bronchoscopy failed or the size of trachea was larger than 20 mm.[7,12] Prior to March 2014, TGAF patients were treated exclusively with covered metallic stents because silicon stents were not approved for the Chinese market. Stent size was determined based on mediastinal window on chest CT and bronchoscopic imaging.[1,10] The diameters of the stents were 10–20% larger than the diameters of the corresponding trachea or main bronchus. The edges of the stents extended approximately 15–20 mm beyond the fistulas.[1,12] Stent shape was chosen depending on the size and location of fistulas. Straight stents were adopted for patients with fistulas in the upper third of the trachea and small fistulas in the middle third of the trachea. Large Y-shaped stents were used for patients with fistulas in the lower third of the trachea, carina, right main bronchus, upper half of left main bronchus, and large fistulas in middle third of the trachea. Small Y-shaped stents were chosen when the fistula was located in the lower half of left main bronchus and right intermedius. L-Shaped stents were chosen when the fistula was located at the middle of the left main bronchus.[1] Silicon stents can be removed by standard grabbing forceps through a rigid bronchoscope under general anesthesia. Metallic stents can be pulled up through recycle-line under flexible or rigid bronchoscopy.

Post-treatment evaluation

All patients received nebulization with a combination of saline and sodium bicarbonate after airway stenting. An iodinated-water contrast swallow test was performed between the 5th and 7th day post-treatment to check potential leaks prior to resuming oral intake. Bronchoscopy was performed to evaluate the situation of stents. Patients were followed up at 1, 3, and 6 months after hospital discharge, or based on their symptoms. Follow up was more frequent in those patients with clinical signs or symptoms of complications. Telephone follow up was made by the referring doctors if patients could not visit doctors routinely. The same patient was evaluated by KPS score at 1 month follow up.

Effectiveness analysis

The primary endpoint was the healing of TGAF, defined as closure of the orifice confirmed by upper gastrointestinal radiography after stent removal.[6] The secondary endpoint was the complete sealing of TGAF, defined as follows: no cough upon drinking water; no contrast flow into the airway under iodinated-water esophagography; and correct position of stents, with or without the persistence of an orifice.[6]

Statistical methods

Statistical analysis was performed using SPSS 20.0 software. Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as numbers and percentages. The relationship between categorical variables was assessed using the Chi-square test. The connection between a qualitative and a quantitative variable was evaluated using Student's t test or the ANOVA test. A logistic regression model was used to identify independent predictive factors influencing the response to endoscopic treatment. Statistical significance was set at $p < 0.05$.

Results

A total of 58 patients (47 male and 11 female) with TGAF were finally included for analysis from January 2013 to January 2018, with a mean age of 61.1 ± 9.3 years (38–73 years). Baseline characteristics are shown in Table 1. Postprandial cough and supine cough appeared approximately 75 days (2–540 days) after esophagectomy; 30 (51.7%) patients had received thoracic radiotherapy at diagnosis, and 19 (32.8%) had undergone chemotherapy. Among the TGAF patients, 10 (17.2%) underwent the Sweet procedure, 14 (24.1%) the Ivor Lewis procedure, 14 (24.1%) the McKeown procedure, and 20 (34.5%) the endoscopic McKeown procedure. Of the 48 (82.8%) patients who presented with pulmonary complications related to fistulas, 48 had aspiration pneumonia, 8 had chronic obstructive pulmonary disease (COPD) exacerbation, and 3 had invasive ventilation due to respiratory failure.

Table 1. Patient characteristics ($n = 58$).

Characteristics	Number
Male/Female	47/11
Age (years)	61.1 ± 9.3
Previous Therapy	
Radiotherapy	30
Chemotherapy	19
Operation procedure	
Sweet	10
Ivor Lewis	14
McKeown	14
Endoscopic McKeown	20
Comorbidities	
COPD	33
Diabetes	4
Hypertension	16

COPD, chronic obstructive pulmonary disease.

Fistula characteristics

Of the total population of patients, 33 (56.9%) had thoracogastric-tracheal fistulas, 8 (13.8%) had thoracogastric-carinal fistulas, 10 (17.2%) had thoracogastric-left main bronchial fistulas, 5 (8.6%) had thoracogastric-right main bronchial fistulas, and 2 (3.4%) had thoracogastric-right intermediate bronchial fistulas. Tracheal stenosis occurred in two patients. The length of orifices was 11.6 ± 7.3 mm (4–30 mm); 37 patients had small

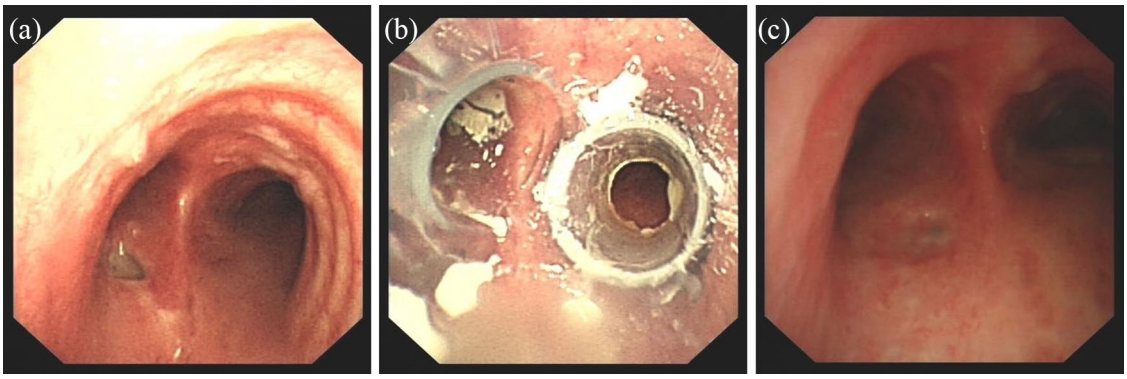

Figure 1. A typical case of healing: tracheal orifice in a patient who undergone thoracic surgery because of esophageal cancer. (a) A TGAF (approximately 0.7 cm in size) was located at the border of trachea and left main bronchus. (b) The fistula was covered by a Y-shaped airway silicon stent under bronchoscopy. (c) The Y-shaped airway silicon stent was removed 3 months later, and healing was observed under bronchoscopy.
TGAF, Thoracogastric-airway fistula.

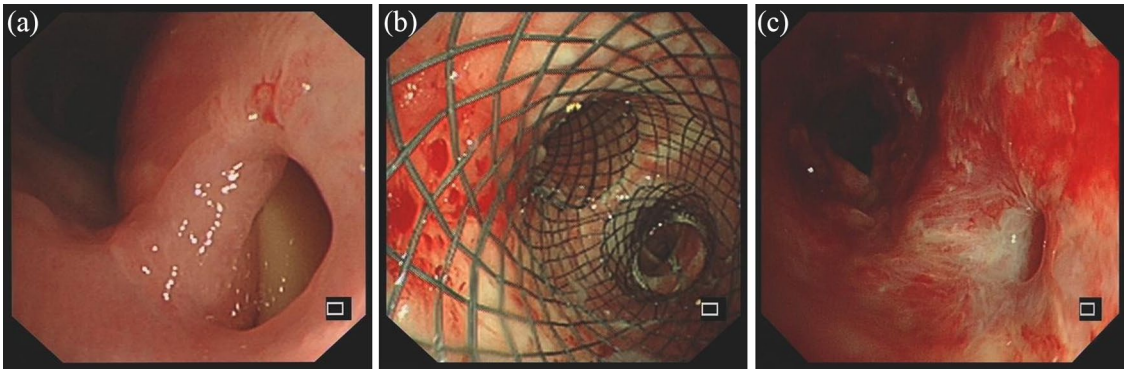

Figure 2. A typical case of complete sealing: Left main bronchial orifice in a patient who undergone thoracic surgery because of esophageal cancer. (a) A TGAF (approximately 0.6 cm in size) was located at the left main bronchus. (b) The fistula was covered by a Y-shaped airway metallic stent under rigid bronchoscopy. (c) The Y-shaped airway metallic stent was removed 6 months later, and the fistula was observed under bronchoscopy. The metallic stent was placed again.
TGAF, Thoracogastric-airway fistula.

orifices and 21 patients had large orifices. The pathological nature of the mucosa surrounding the fistula orifice was malignant in 26 patients, and nonmalignant in 32 patients.

Characteristics of airway stenting

Straight covered metallic stents were used in 7 (12.1%) patients, straight silicon stents in 5 (8.6%) patients, L-shaped covered metallic stents in 3 (5.2%) patients, large Y-shaped covered metallic stents in 21 (36.2%) patients, large Y-shaped silicon stents in 17 (29.3%) patients, and small Y-shaped covered metallic stents in 5 (8.6%) patients.

Effectiveness of airway stenting

Healing was achieved in 34.5% of the cases ($n=20$) with a mean time of 7.1 ± 3.6 months (3–12 months). There was no significant difference ($p=0.517$) in healing rate between patients with covered metallic stents (12/36, 33.3%) and those with silicon stents (8/22, 36.4%). Complete sealing was achieved in 45 (77.6%) patients. There was also no significant difference ($p=0.325$) in complete sealing rate between patients with covered metallic stents (29/36, 80.6%) and those with silicon stents (16/22, 72.7%). Typical cases of healing and complete sealing are shown in Figure 1 and Figure 2, respectively. Pulmonary infection was effectively controlled, cough relieved, sputum decreased

Table 2. The KPS and respiratory manifestations before and after airway stenting.

Variable	Before stenting	After stenting	*p* value
KPS	50.0 ± 14.0	74.0 ± 19.0	$<10^{-3}$
Cough	58/58 (100%)	10/58 (17.2)	$<10^{-3}$
Pulmonary infection	48/58 (82.8%)	8/58 (13.8%)	$<10^{-3}$

KPS, Karnofsky performance Score.

gradually, and the KPS increased significantly after airway stenting. The data are listed in Table 2. The clinical manifestations also improved in 13 (22.4%) patients with incomplete sealing.

The patients were followed up for 2–61 months; 30 patients died of organ failure associated with recurrent and advanced carcinoma 3–18 months later (mean 8.4 ± 4.3 months), and 16 died of respiratory failure 4–37 months later (mean 11.0 ± 9.3 months). Two patients died of massive hemoptysis at 2 and 3 months after stenting. One patient died of massive upper gastrointestinal hemorrhage at 2.5 months after stenting. Seven patients were still alive and eating normally at the end of follow up (4–61 months). Two patients were lost to follow up.

Factors associated with healing

In univariate analysis, the factors associated with healing included nonmalignant fistulas, with no previous history of radiotherapy or chemotherapy, small fistulas, and shorter postesophagectomy duration ($p < 0.05$). The data linked to healing are summarized in Table 3. In multivariate analysis, only shorter postesophagectomy duration was associated with healing (OR 1.135; 95%CI: 1.0–1.289; $p = 0.04$).

Complications

All patients developed retention of secretions and varying degrees of granulation tissue formation. Typical images are shown in Figure 3. Interventional bronchoscopy was used to treat these complications. Migration occurred in two cases with straight silicon stents, and in one case with straight metallic stent. This displaced metallic stent was replaced by a Y-shaped metallic stent, and two silicon stents were repositioned and fixed externally. No subsequent migration was observed.

Discussion

TGAF is a serious complication in esophageal cancer patients undergoing esophagectomy. Healing or sealing TGAF can relieve symptoms, reduce complications, and improve patients' survival and quality of life. Airway stenting can effectively separate airway and thoracic stomach, permitting oral feeding and reducing bronchial contamination. We found that all healing cases were nonmalignant TGAFs. In addition, TGAF was more prone to heal with earlier diagnosis and treatment.

Healing the fistula is the primary therapeutic objective of TGAF. However, it is very difficult for patients with malignant fistulas because of the local invasion and wide spread of cancer.[13] Based on previous studies, small orifices were expected to have a higher healing rate than large ones in nonmalignant esophagorespiratory fistulas.[6] This was also confirmed in the present study. More importantly, we also discovered that TGAF with a shorter postesophagectomy period was achieved healing more easily. Early TGAF is usually nonmalignant, which is associated with the injury of tracheobronchial membranous wall during an esophagectomy and gastric ischemic necrosis.[14,15] Late TGAF, which occurs following tumor recurrence, chemotherapy, radiotherapy and uncontrolled inflammation, is mostly malignant.[1,16] Delayed management can lead to excessive leaking of stomach contents, thereby causing damage to airway walls and expansion of orifices.[17]

Tracheoesophageal fistula is reported in approximately 6% of patients receiving chemotherapy. The incidence jumps to 73.9% when chemotherapy is combined with radiotherapy.[13,18] We also found that lack of a history of chemotherapy and radiotherapy was related to TGAF healing. Radiotherapy and chemotherapy might promote the development of a fistula by lysing the tumor, thereby reducing the probability of healing.[19,20]

Table 3. Patients features and results of bronchoscopic stenting.

	Healing group	No healing group	*p* value
Number	20	38	
Male	15	32	0.558
Smoking	18	32	0.543
COPD	14	17	0.144
Diabetes	1	3	0.679
Hypertension	8	8	0.125
Operation procedure			
Sweet	4	6	0.687
Ivor Lewis	6	8	0.449
McKeown	7	7	0.161
Endoscopic McKeown	10	10	0.071
Previous therapy			
Radiotherapy	2	28	$<10^{-3}$
Chemotherapy	3	16	0.037
Malignant fistulas	0	26	$<10^{-3}$
Postesophagectomy duration (days)	9.5 ± 6.5	218.0 ± 613.0	$<10^{-3}$
Small fistulas	3	18	0.015

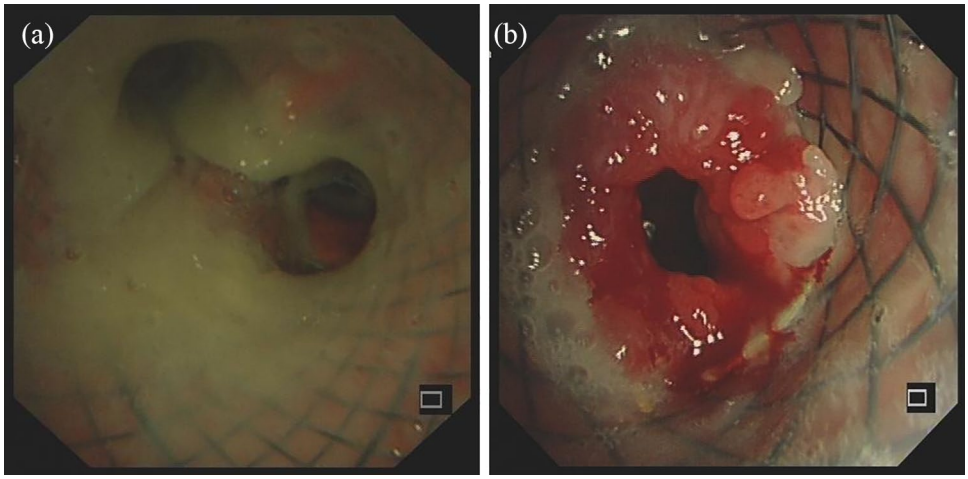

Figure 3. Complications in patients with airway stents. (a) Massive secretions attached to a metallic stent. (b) Granulation tissue was observed at the edge of stent.

An airway stent can be implanted under fluoroscopy and bronchoscopy.[1,4] Flexible and rigid bronchoscopy provide a direct observation of airway stricture and stent position, allow more pneumologists to perform stent implantation, and avoid radiation exposure. Silicone stents are designed to be placed only using a rigid bronchoscope. Airway stenting under fluoroscopy can provide visualization of stent release. Bronchoscopy under fluoroscopic guidance is also usual used in clinical practice.

Complete sealing of the TGAF is also important for a better prognosis. Sealing the TGAF can effectively reduce the risk of aspiration pneumonia, relieve coughing, and restore oral feeding.[1,12] Covered metallic stents and silicon stents are most commonly used to treat airway fistula.[1,12,21,22] Metallic stents can adapt well to tortuous airways because of their self-expandable properties; however, they also hold potential disadvantages, such as metal fatigue and membrane damage.[4,21] Silicon stents have the advantage of durability and easy removal; however, their placement depends on rigid bronchoscopy and general anesthesia. The use of the silicon stents in TGAF has been described only in case reports or small single center series.[21] In addition, few studies have made comparisons between covered metallic stents and silicon stents in the same research. Our study showed that both metallic and silicon stents were effective in sealing TGAF in a complete way. The individualized airway stent is necessary to seal fistula completely due to variations in airway diameter, shape, and neighboring anatomic structure.[22,23] An advantage of silicon stents is customization in situ. Covered metallic stents can be individualized by the manufacturer only prior to stenting. Our results support the view that both silicon and metallic stents are effective approaches to sealing TGAF. Development of new and efficient techniques and devices may further help to heal or completely seal TGAF.[24,25]

There are some limitations to this study. Firstly, it is a retrospective single-center report, so our results might not be fully consistent with other reports.[1,6,7] Secondly, we do not make a direct comparison in healing and sealing TGAF between airway stents and surgery and gastroscopic treatment.

In conclusion, both silicon and covered metallic airway stents are effective to close TGAF. A shorter postesophagectomy period may predict a higher healing rate in TGAF patients. Early diagnosis and treatment will help improve the prognosis of TGAF.

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Authors Hongwu Wang and Meimei Tao contributed equally.

Author contributions

H Wang and M Tao were involved in conception and design, collection and assembly of data, data analysis and interpretation, and manuscript writing. N Zhang, H Zou, D Li and Y Zhou were involved in collection and assembly of data and review. H Wang approved the final version of the manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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