Brief Report

Pilot study of incidence of gastroesophageal reflux after lung resection

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Abstract: Patients undergoing lung resection may be at risk of gastroesophageal reflux (GER) and silent aspiration following surgery. Defining high-risk patients may lead to prevention strategies for silent aspiration and subsequent exacerbation of underlying pulmonary disease. A pilot study of 50 patients was performed to investigate postoperative gastroesophageal reflux disease (GERD) symptoms and the pepsin concentration in saliva. Patients answered a questionnaire concerning GERD symptoms before lung surgery and at the time of discharge. Saliva samples were obtained before surgery, on the third postoperative day and at discharge. Pepsin concentration was measured with Peptest. The pepsin concentration in saliva following resection was significantly elevated on postoperative day 3, but it returned to the baseline level at discharge. Patients undergoing resection of four or more lung subsegments had a continuously elevated pepsin concentration in saliva on postoperative day 3 [mean difference 65.63 ng/mL, 95% confidence interval (CI): 9.130–122.1] and at discharge (mean difference 76.22 ng/mL, 95% CI: 19.72–132.7). Patients with a >10% reduction of forced expiration volume in one second also had a continuous elevated pepsin concentration from the 3rd postoperative day. Lung resection resulted in elevated pepsin concentration in the saliva, which persisted in patients who received resections equivalent to or more than right middle lobectomy in volume. Resection of large volumes of lung may lead to anatomical changes and changes in breathing patterns and result in GER.

Keywords: Lung resection; pepsin; gastroesophageal reflux (GER); Peptest; Frequency Scale for the Symptoms of GER disease (FSSG)

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Introduction

Interstitial lung disease and chronic obstructive pulmonary disease (COPD) frequently coexist in patients undergoing lung surgery for lung tumors. Understanding and preventing factors associated with disease progression and exacerbation may lead to improved prognosis in these patients. Studies on idiopathic pulmonary fibrosis (IPF) have reported higher inflammatory cytokines such as interleukin-14 (1), epithelial-mesenchymal transition following injury due to defective alveolar type-II cells (2) and dietary intake such as alcohol and beef (3), to be associated with pathogenesis and disease progression.

Patients with lung disease reportedly have a high incidence of gastroesophageal reflux disease (GERD). Changes in breathing or swallowing patterns, excess negative thoracic pressure, and changes in lower esophageal sphincter (LES) pressure are causes of GERD and silent aspiration in these patients (4,5).

In 2005, Sawabata *et al.* (6) reported that 33% of patients developed gastroesophageal reflux (GER) symptoms

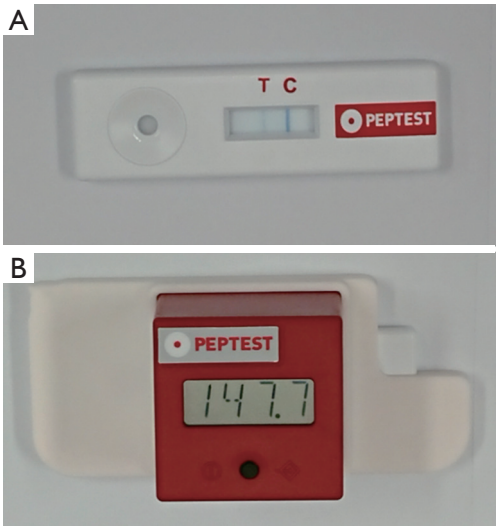

Figure 1 Peptest® strip and cube. (A) The Peptest® strip is used to assess for the presence of pepsin in saliva. (B) The Peptest® cube is suitable for use in the quantitative and qualitative evaluation of Pepsin measurement results and will display the result of pepsin concentration directly in ng/mL in just three seconds.

within 1 year of lung resection. Another author found that elevation of the diaphragm or loss of lung volume could cause these symptoms (6). Silent aspiration associated with GERD may exacerbate IPF (7). The incidence of acute exacerbation of COPD is reportedly seven times higher in patients with than without GERD (4).

Acute exacerbation of IPF and COPD are major problems in the postoperative period after lung resection. We hypothesized that the anatomical changes and increased negative pressure due to lung volume loss lead to GERD and silent aspiration in the postoperative period, which may be one of the factors associated with acute exacerbation of IPF and COPD. The aim of this study is to reveal the incidence of GERD in patients who have undergone lung resection and to ascertain risk factors of GERD, such as underlying lung disease, operative site and type of resection. This may lead to preventive strategies against GERD and silent aspiration, in turn improving the postoperative course of patients with underlying lung disease. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1794/rc).

Patients and methods

Patients who underwent lung resection for lung tumors were included in this study. The patients answered a clinical questionnaire regarding GER syndrome before surgery and before discharge. The questionnaire used was the Frequency Scale for the Symptoms of GERD (FSSG) (8), which contains questions concerning acid reflux-related symptoms and dysmotility symptoms, with scales according to the frequency of the symptoms. Saliva (1–2 hours after a meal) was collected before surgery, on postoperative days 1 and 3, and before discharge (around 1 week following surgery). The pepsin concentration in the saliva was measured using a Peptest® (RD Biomed Ltd., Cottingham, England). Briefly, saliva samples were collected into tubes containing citric acid and stored at 4 ℃ until assay (within 1 week). Next, 0.5 mL of the sample was centrifuged, and 80 µL of supernatant was mixed with a migration buffer; 80 µL of this mixture was applied to a lateral flow device containing two monoclonal antibodies against pepsin. Pepsin-positive samples were identified by the appearance of two blue lines after 5 to 15 minutes. The pepsin level was assessed at 15 minutes with an electronic reader (RD Biomed Ltd.) (*Figure 1*). Patient background and pulmonary function test (PFT) results before surgery and 1 month following surgery were recorded. The baseline computed tomography (CT) findings were screened by two respirologists (T.S. and Y.T.). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the ethics board of the International University of Health and Welfare, Atami Hospital (No. 18-A-124). Written informed consent was obtained from all patients participating in the study. The patient inclusion criteria were treatment by lung resection surgery, the ability to provide written informed consent, and an age of >20 years. The exclusion criteria were gastric or esophageal surgery, evident gastric herniation on CT, and other causes of ineligibility for participation. The primary endpoint of this study was the frequency of GER following lung resection. The secondary endpoints were the pepsin positivity rate in saliva by type of surgery and the relationship with underlying lung disease, PFT results, and the pepsin positivity rate. Statistical analysis was performed with GraphPad Prism (GraphPad Software, San Diego, CA, USA). Paired *t*-tests were performed for changes in FSSG and pepsin concentration in saliva preoperatively and at discharge. One-way repeated measure analysis of variance (ANOVA) was used for analysis in changes in pepsin concentration at all time points and Two-way repeated measure ANOVA for pepsin concentration according to resected number of subsegments. Dunnett's multiple

Table 1 Baseline patient characteristics

Characteristics	Values (n=50)
Type of lung resection, n (%)	
Bilobectomy	1 (2.0)
Lobectomy	15 (30.0)
Segmentectomy	25 (50.0)
Wedge resection	9 (18.0)
Diagnosis, n (%)	
Lung cancer	43 (86.0)
Metastatic lung tumor	1 (2.0)
Benign lung tumor	6 (12.0)
Smoking history, n (%)	
Current-smoker	11 (22.0)
Ex-smoker	22 (44.0)
Non-smoker	17 (34.0)
Background computed tomography (baseline), n (%)	
Normal	33 (66.0)
Emphysema	13 (26.0)
Emphysema + fibrosis	4 (8.0)
Pulmonary function test, n (%)	
Normal	32 (64.0)
Obstructive	13 (26.0)
Restrictive	3 (6.0)
Mixed	2 (4.0)

comparison test was performed when comparing each time point with the preoperative value. A P value of <0.05 was considered statistically significant.

Results

Fifty-five patients were enrolled, among whom 50 patients were considered eligible for analysis. The 5 excluded patients had a history of contralateral lung resection. Of the 50 patients analyzed, 25 were male and 25 were female. The patients' ages ranged from 43 to 90 years (mean, 71.4 years). Patient characteristics is shown in *Table 1*.

There was no significant difference in GERD-associated symptoms before and after lung resection (multiple *t*-test) (*Figure 2A*). The pepsin concentration in saliva following resection was significantly elevated on postoperative day 3 (P=0.009, one-way repeated-measures ANOVA and Dunnett's multiple comparison test) (*Figure 2B*), but it returned to the baseline level at discharge. Thirteen patients (26.0%) had newly acquired GERD at the time of discharge, when comparing preoperative values (pepsin cutoff level 76 ng/mL). In patients who underwent resection of four or more subsegments of lung, the pepsin concentration compared with the preoperative level remained significantly elevated at the time of discharge (P=0.005, two-way repeated-measures ANOVA and Dunnett's multiple comparison test) (*Figure 2C*). Patients with a ≥10% reduction in the forced expiratory volume delivered in one second (FEV1.0) postoperatively had a significant elevation of the pepsin concentration in saliva both on postoperative day 3 and at discharge (multiple *t*-test) (*Figure 3A*). There was no significant association of the surgical site (left or right) (*Figure 3B*) with continued pepsin elevation, but patients with an obstructive disorder as shown by PFT and emphysema on baseline lung CT (*Figure 3C*) had a significantly elevated pepsin concentration at the time of discharge (*Figure 3D*). There were no significant differences in the patients' baseline characteristics (age, sex, smoking history, baseline lung CT findings, PFT results, surgical site) between patients who underwent resection of fewer than four lung subsegments and those who underwent resection of four or more lung subsegments.

Discussion

Studies concerning structural changes following lung resection have reported mediastinal shift and elevation of the diaphragm according to the resected lobe (9) and new hiatal hernias, especially after lobectomy (10). Hiatal hernia is associated with GERD and is also reported to be a risk factor for postoperative complications in patients undergoing lobectomy (11).

No studies have focused on the actual incidence of and risk factors for GER following lung resection except for studies utilizing questionnaires on reflux symptoms (6,12). In a recent study on persistent cough after pulmonary resection, 36.9% of patients with persistent cough had GER diagnosed by Reflux Diagnostic Questionnaire, whereas 12.2% of non-cough patients had GER (13), making a total of 18.6% of post-lung surgery patients diagnosed with GER. The standard procedure for studying GER is 24-hour pH monitoring of the esophagus. A study on chronic cough following lung resection showed that patients with a nonproductive cough in the postoperative period had a high

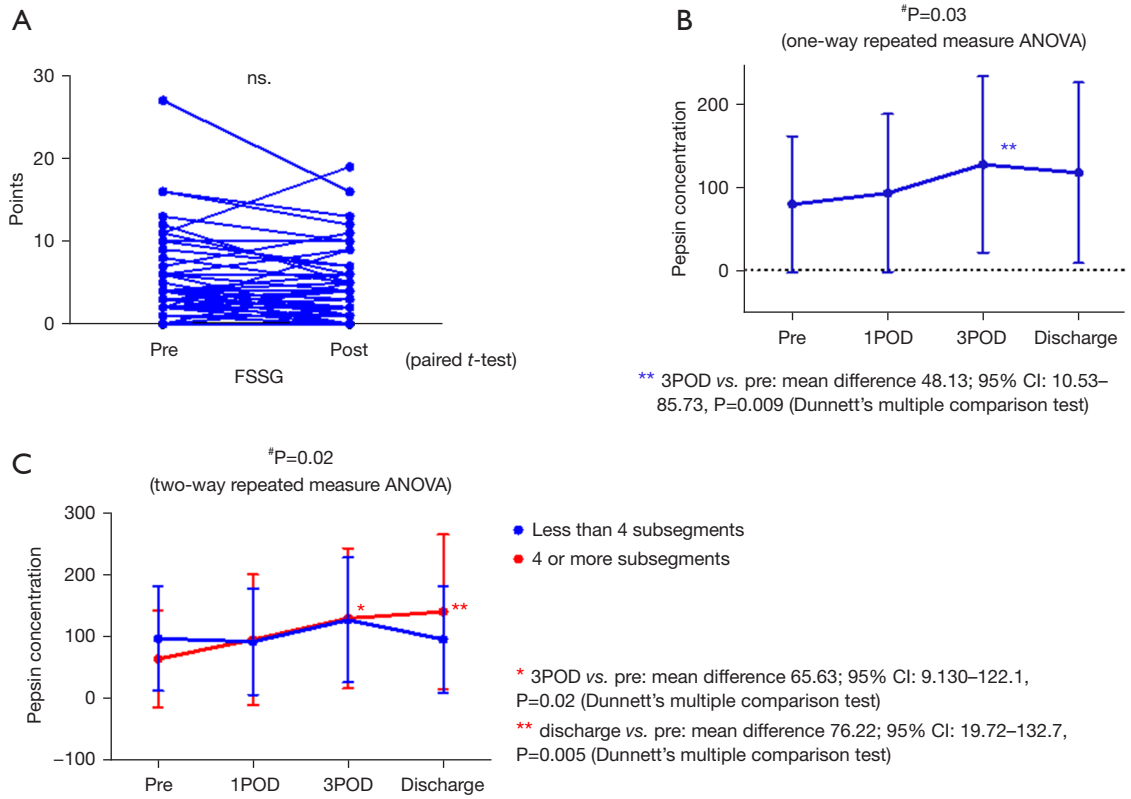

Figure 2 Perioperative changes in GER symptom and pepsin salivary concentration. (A) Changes in gastroesophageal reflex symptoms quantified with FSSG. (B) Changes in pepsin concentration in oral secretion. #, one-way repeated-measures ANOVA. (C) Changes in pepsin concentration in oral secretion stratified according to number of resected subsegments. #, two-way repeated-measures ANOVA. Error bars, standard deviation; FSSG, Frequency Scale for the Symptoms of GERD; pre, pre-operation; post, post-operation; ns, not significant (paired *t*-test); POD, post-operative day; GERD, gastroesophageal reflux disease; ANOVA, analysis of variance; CI, confidence interval; ns, not significant.

probability of GER on 24-hour pH monitoring (12).

Studies on the incidence of silent aspiration and graft rejection have been performed in lung transplant recipients. Esophageal 24-hour impedance/pH monitoring and measurement of the pepsin and bile acid levels in bronchoalveolar lavage fluid (BALF) revealed acidic or non-acidic GER in 48% of patients and pepsin in the BALF of all patients, indicating the presence of silent aspiration in lung transplant patients. Significantly more patients had detectable bile in the BALF among the bronchiolitis obliterans cohort (14).

Obtaining BALF from patients in the early postoperative period is highly invasive and may put the patient at risk for exacerbation of COPD or interstitial lung disease. A pilot study of pepsin in tracheal and oral secretions was performed as a way to screen patients at risk of silent aspiration. Twenty percent of critically ill patients had pepsin-positive oral secretions, while 4% had pepsin-positive tracheal secretions. The authors concluded that additional intervention to prevent reflux and aspiration in patients with pepsin-positive oral secretions may prevent aspiration-associated pneumonia in these patients (15). The Peptest® is a device containing human monoclonal antibodies that detect and capture pepsin protein, with a lower limit of detection of 16 ng/mL and an upper limit of 500 ng/mL. In a study of 285 subjects who underwent 24-hour multichannel intraluminal impedance/pH monitoring and upper gastrointestinal endoscopy, salivary pepsin detection with the Peptest® had a sensitivity of 73% and specificity of 88.3% for diagnosing GERD at a cut-off value of 76 ng/mL (16). Another recent study placed the cut-off value at 31.4 ng/mL with a sensitivity of 86.7% and specificity of 66.0% (17). Although the diagnostic value of the Peptest® still remains controversial among authors (18), it is easy to perform and noninvasive, and it may be a useful device to screen patients at high risk of silent aspiration.

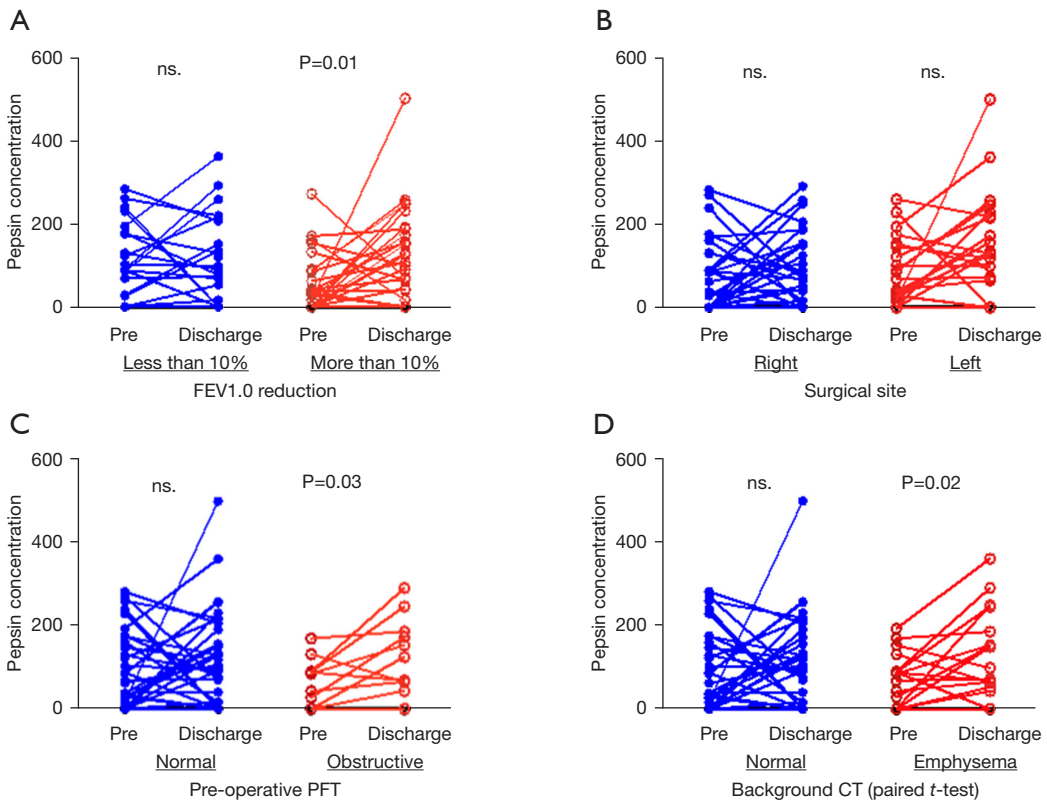

Figure 3 Perioperative changes in pepsin salivary concentration according to reduction pulmonary function and patient background. (A) Changes in pepsin concentration according to postoperative FEV1 reduction; (B) changes in pepsin concentration according to surgical site; (C) changes in pepsin concentration according to preoperative pulmonary function; (D) changes in pepsin concentration according to background CT findings of the lung (paired *t*-test). FEV1, forced expiratory volume in one second; PFT, pulmonary function test; pre, pre-operation; ns, not significant (paired *t*-test); ns, not significant; CT, computed tomography.

In this study, the patients had an elevated pepsin concentration in oral secretions on the third postoperative day after lung resection, and the pepsin concentration returned to the preoperative value at the time of discharge. In patients who underwent resection of four or more subsegments of lung, which is equivalent to a right middle lobectomy, the pepsin level remained elevated at the time of discharge.

In a manometric study of patients with normal LES pressure, exaggerated ventilatory effort with exercise or respiratory disease led to a high thoracoabdominal pressure gradient and increased esophageal acid exposure. In that report, the authors stated that delayed gastric emptying and diminished salivation were additional factors associated with GER (19).

The elevated pepsin found on postoperative day 3 in the present study may have been associated with decreased gastric motility and salivation following general anesthesia. The increase in the pepsin level at discharge may have been associated with the decrease in FEV1.0 and increased ventilatory effort due to volume loss and changes in breathing patterns. Major volume changes may lead to increased negative pressure and dynamic structural changes leading to changes in LES pressure. Patients undergoing major resections, such as lobectomy, may be at high risk of GERD and silent aspiration.

Patients at high risk of silent aspiration may benefit from a dietary change, the use of Fowler's position following surgery, and intensified pulmonary rehabilitation (PR).

The role of PR in patients with postoperative GER has yet to be studied. Prospective controlled studies on training of inspiratory muscles have revealed improvements in GER symptoms, decreased acid exposure, and increased LES pressure (20). PR may also improve breathing patterns, breathing effort, and excessive negative intrathoracic pressure in the postoperative period.

The main limitations of this study are that it was a small-scale study from a single institution with no control group and a wide range of surgical procedure. The method used to detect GER was also not a standard procedure. Further analysis of structural changes and manometric measurements may establish the causal relationship between lung resection and GERD. Additionally, the number of patients who actually developed silent aspiration could not be identified in this study. Studies that involve more patients and examine other parameters, such as bile in tracheal secretion and esophageal/laryngeal pH monitoring, may provide further insight into the risk of silent aspiration and its association with postoperative morbidity as well as the effectiveness of prevention strategies.

Conclusions

Patients undergoing lung resection have an elevated pepsin concentration in oral secretions in the early postoperative period. Patient undergoing resections of lung volume equivalent to or more than middle lobectomy may have persistent regurgitation following surgery. Further studies may elucidate the risk factors for silent aspiration and exacerbation of underlying interstitial lung disease, which may lead to prevention strategies in high-risk patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1794/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1794/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1794/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was reviewed and approved by the ethics board of the International University of Health and Welfare, Atami Hospital (No. 18-A-124). Written informed consent was obtained from all patients participating in the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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