

Acid and Duodenogastroesophageal Reflux after Esophagectomy with Gastric Tube Reconstruction

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- OBJECTIVE:** Patients who undergo esophagectomy with gastric tube reconstruction incur increased risk for acid reflux and duodenogastroesophageal reflux. Few postesophagectomy studies of gastroesophageal reflux disease have included simultaneous 24-h pH and bilirubin monitoring. The aim of this study is to evaluate acid reflux and duodenogastroesophageal reflux after esophagectomy with gastric tube reconstruction.
- METHODS:** Reflux symptom evaluation, endoscopy, and simultaneous 24-h pH and bilirubin monitoring in the cervical esophagus were performed in 25 patients who underwent Ivor Lewis esophagectomy, intrathoracic esophagogastrostomy, and digital dilation of the pyloric ring as treatment for esophageal cancer.
- RESULTS:** Reflux symptoms were severe, mild, and absent in 2, 7, and 16 patients, respectively. Reflux esophagitis and Barrett's esophagus was observed in 11 and 1 patients, respectively. Elevated acid reflux occurred in 7 patients (28%). Elevated duodenogastroesophageal reflux was recorded in 11 patients (44%). Reflux profile analysis identified three patterns: 4 subjects (16%) with both elevated acid reflux and duodenogastroesophageal reflux; 3 (12%) with only elevated acid reflux; and 7 (28%) with only elevated duodenogastroesophageal reflux. Of 7 patients with only elevated duodenogastroesophageal reflux, 4 developed reflux esophagitis. Although reflux symptoms did not correlate with endoscopic esophagitis, a significant correlation was observed between endoscopic esophagitis and acid reflux and/or duodenogastroesophageal reflux.
- CONCLUSIONS:** Reflux symptoms represented a poor indication of esophagitis in patients with esophagectomy and gastric tube reconstruction. Simultaneous 24-h pH and bilirubin monitoring can help in identifying patients at high risk for reflux esophagitis, as well as indicating the cause of esophagitis.

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INTRODUCTION

Early detection of malignant lesions and refinements in surgical technique and perioperative management have significantly improved survival after esophagectomy for esophageal cancer (1-4). Enhanced survival, in turn, highlights the need to evaluate and maintain quality of life for postesophagectomy patients. Factors affecting quality of life after esophagectomy include dysphagia, heartburn, regurgitation, early satiety, fatigue, and psychological problems. Among these, reflux symptoms have critical implications because gastroesophageal reflux can have devastating consequences such as aspiration pneumonia, bleeding, recurrent stricture, and columnar epithelial metaplasia (Barrett's esophagus), which can give rise to adenocarcinoma. Although many studies have considered postesophagectomy gastroesophageal reflux disease (5-11), relationships among reflux symptoms, endoscopically evident esophagitis, and esophageal exposure

to acid and duodenal juice after esophagectomy have not been fully identified.

Patients who undergo esophagectomy with gastric tube reconstruction remain at increased risk for prolonged esophageal exposure to gastric acid and duodenal juice because normal antireflux mechanisms (the lower esophageal sphincter, angle of His, and phrenoesophageal ligament) have been resected or disrupted. In addition, gastric drainage procedures may promote duodenogastric reflux, leading in turn to bile reflux into the esophagus. Furthermore, negative intrathoracic pressure and positive intraabdominal pressure act together to promote reflux across the anastomosis. In this context, such postesophagectomy patients are informative subjects for studying the effects of esophageal exposure to acid and duodenal juice in the causation of esophageal mucosal injury and development of columnar metaplasia. However, reflux patterns and their prevalence and implications for esophagitis remain unclear. Few detailed clinical

reports have examined acid and duodenogastroesophageal reflux (DGER) using simultaneous pH and bilirubin monitoring after esophagectomy (8, 11).

Establishing the cause of reflux esophagitis after esophagectomy using combined esophageal pH and bilirubin monitoring may permit identification of patients at high risk for reflux esophagitis and Barrett's esophagus, refining indications for prophylactic measures after gastric pull-up esophagectomy, and facilitating comparison between reconstruction methods in patients expected to survive for a long time after esophagectomy. The aims of the present study were three-fold: to determine correlations among reflux symptoms, endoscopic findings in the cervical esophagus, and acid reflux and DGER determined by combined monitoring after esophagectomy with gastric tube reconstruction; to identify reflux patterns and determine the prevalence of each; and to determine the significance of each pattern in causation of esophageal mucosal injury.

PATIENTS AND METHODS

Patients

Twenty-five patients who underwent Ivor Lewis esophagectomy and gastric tube reconstruction for thoracic esophageal squamous cell carcinoma in our department between 1997 and 2002 were enrolled. The patients (23 men and 2 women) with a mean age of 65 ± 8 yr (range: 53–79 yr) were evaluated by reflux symptoms, endoscopy and simultaneous pH, and bilirubin monitoring. Patients who underwent gastric tube reconstruction through the antesternal or retrosternal route, or had an esophagogastrostomy constructed in the neck or lower thorax were excluded from this study. None of the patients had symptoms consistent with delayed gastric emptying. Although some patients had reflux symptoms, no patients had received medication to suppress gastric acid secretion or stimulate gastric motility since esophagectomy.

Surgical Procedure

The abdomen was explored through an upper midline incision. Kocher's mobilization of the duodenum was performed in all patients. After perigastric and celiac lymph node dissection, the gastric tube was constructed using a linear cutting stapler (Proximate Linear Cutter 55, Ethicon Endo-Surgery, Cincinnati, OH). The stapler was fired as many times as needed to divide the stomach from the lesser curvature at the anastomosis between the right and left gastric arteries along the axis of the greater curvature, creating a 7-cm wide tube. Digital dilatation of the pyloric ring was performed. A right thoracotomy provided access for dissection of the thoracic esophagus and mediastinal lymph nodes. The gastric tube was placed in the posterior mediastinum, and an intrathoracic esophagogastrostomy was performed at the level of the thoracic inlet (2 cm inferior to the origin of the right subclavian artery) on the anterior wall of the gastric tube using a circular stapling device (Premium Plus CEEA 25, USSC,

Auto Suture Company, Norwalk, CA). Cervical lymph node dissection was performed in 9 patients.

Symptoms

Reflux symptoms, such as pharyngeal regurgitation, cervical heartburn or pain, and throat discomfort associating sleep disturbance or nocturnal cough was assessed as follows: absent, mild (can be ignored or cannot be ignored but does not affect lifestyle), and severe (affects lifestyle that includes inability to lie flat contributing to sleep deprivation).

Endoscopy

Preoperative endoscopy had confirmed that the squamous epithelium in the cervical esophagus was normal in all patients and that Barrett's epithelium was absent. Postoperative endoscopy was performed less than 1 month before or after the pH and bilirubin monitoring to observe mucosal changes in all patients. Reflux esophagitis was graded according to the Los Angeles Classification System (12). The mean interval between esophagectomy and endoscopic examination was 24 ± 27 months (range: 4–70 months, median: 12.8 months).

Combined Ambulatory 24-h Esophageal pH and Spectrometric Bilirubin Monitoring

Simultaneous esophageal pH and bilirubin monitoring was performed for 24 h. Medications known to affect gastric acid secretion and motility were withheld following esophagectomy. An antimony catheter with two sensors for pH (Medtronic, Skovlunde, Denmark) was calibrated in buffer solutions of pH 7 and pH 1 before each study. Then, after the catheter was passed transnasally, proximal and distal pH sensors, respectively, were positioned 2 cm above and 8 cm below the esophagogastrostomy identified fluoroscopically by the presence of staples. Proximal esophageal pH and distal gastric tube pH were recorded by a portable digital data recorder (Digitrapper Mark III, Medtronic) that stored pH data every 4 s for 24 h. Data were downloaded into a personal computer for analysis using EsopHogram Reflux Analysis software (Medtronic). An esophageal pH value below 4.0 was defined as acid reflux. Although no normal values for acid reflux after esophagectomy have been established, elevated acid reflux was defined as an esophageal pH below 4.0 for more than 4.4% of the monitoring time (13). Esophageal bilirubin monitoring was performed using a fiberoptic sensor (Bilitec 2000, Medtronic) that stored bilirubin absorbance data every 8 s. The fiberoptic probe was calibrated in water, and then was placed 2 cm above the esophagogastrostomy at the same level as the proximal pH sensor, to simultaneously measure bilirubin in the cervical esophagus. Esophageal bilirubin exposure was measured by spectrometry based on the specific light absorption of bilirubin at a wavelength of 453 nm, which was recorded by a portable optoelectronic data recorder (14). Twenty-four-hour bilirubin absorbance data were analyzed using the Gastrosoft Esophagus Program (Medtronic) to calculate the total time during which light absorbance by bilirubin exceeded 0.14 in the study period. A value exceeding 0.14

was defined as DGER, and elevated DGER was defined as bilirubin absorbance exceeding 0.14 for more than 1.8% of the monitoring time (14, 15). To investigate the relationship of acid to bilirubin exposure, moment-to-moment comparison of pH and bilirubin absorbance readings for each reflux event was carried out using a custom-written computer program. Patients were instructed to follow a special diet (500 ml of Ensure Liquid; low-residue diet, Dinabot, Tokyo, Japan) taken 3 times daily at the usual meal times during the monitoring study with only water in addition. The liquid diet had a pH of 6.5. Every patient kept a diary to record dietary intake, symptoms, and time spent in the supine and upright positions. Whether the patients slept with the head of the bed elevated was not recorded. All patients provided informed consent for participation in the study. Although some patients complained of nasal or throat discomfort, all tolerated monitoring. A representative tracing of simultaneous esophageal pH and bilirubin absorbance in a patient with both acid reflux and DGER is shown in Figure 1.

Statistical Analysis

Data are expressed as the mean \pm standard deviation. The Wilcoxon signed-rank test was used to analyze the difference between values in upright and supine positions. Spearman's rank correlation coefficient test was used to evaluate the correlation between esophageal and gastric tube pH, and between percentage of time in which pH was below 4.0 and percentage in which bilirubin absorbance was above 0.14. Fisher's exact test was used to compare proportions. A p -value less than 0.05 was considered to indicate statistical significance. The Stat view computer program (Abacus Concepts, Berkeley, CA) was used for statistical calculations.

RESULTS

Symptoms and Endoscopic Findings

Reflux symptoms were severe, mild, and absent in 2, 7, and 16 patients, respectively. One patient suffered from frequent coughs at night. Barrett's esophagus was observed in 1 patient (4%), while reflux esophagitis was observed in 11 patients (44%; grade A, 2; grade B, 7; and grade C, 2). No ulceration in the gastric tube or duodenum was observed in any patient.

Gastric Tube pH

Considering all patients, percentages of time during which gastric tube pH was below 4.0 and 3.0, respectively, were $41.9 \pm 39.2\%$ (range: 0–95.6%) and $36.9 \pm 37.3\%$ (range: 0–92.4%). The percentage of time during which gastric pH was below 4.0 was more than 10% in 14 patients. Gastric tube pH varied between upright and supine positions.

Esophageal pH and Bilirubin Exposure

The percentage of time during which esophageal pH was below 4.0 correlated significantly with the percentage during which gastric tube pH was below 4.0 ($R = 0.535$, $p < 0.01$; Fig. 2). No correlation was evident between the percentage of time during which esophageal pH was below 4.0 and the percentage during which bilirubin absorbance was exceeding 0.14 ($R = 0.02$, $p = 0.925$; Fig. 3). The mean percentage of time during which esophageal pH was below 4.0 was $3.4 \pm 6.5\%$ (range: 0–30.9%). Elevated acid reflux was observed in 7 of 25 patients (28%). The percentage of time during which esophageal pH was below 4.0 in the supine position ($5.3 \pm 10.2\%$, range: 0–43.8%) was significantly greater than that in the upright position ($0.7 \pm 1.6\%$, range: 0–5.9%, $p < 0.01$).

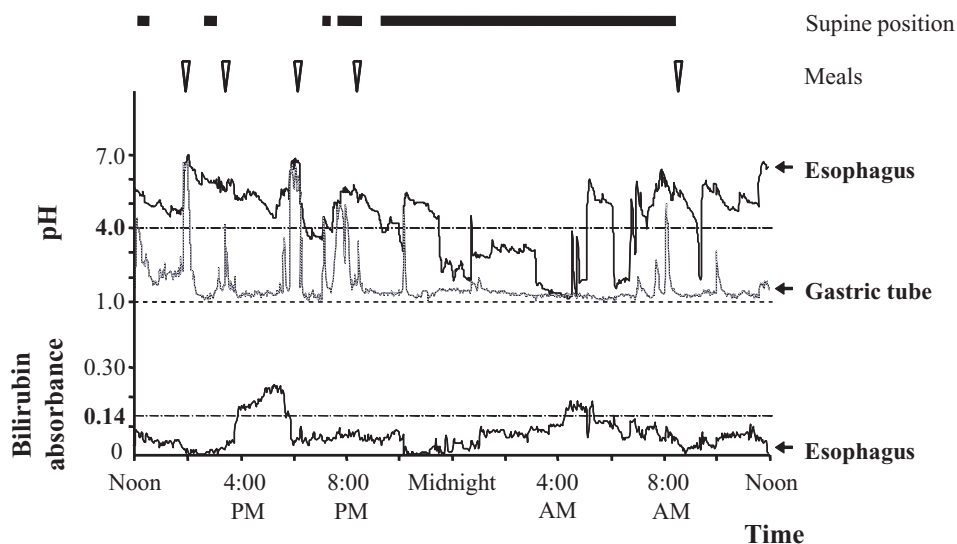


Figure 1. Representative tracing showing simultaneously recorded esophageal pH and bilirubin absorbance in a patient with both acid and DGER. Upper = pH tracing; Lower = bilirubin absorbance tracing. Note that mixed reflux (acidic bilirubin reflux) occurred between 4:00 and 5:00 AM while the patient was supine. On the other hand, bilirubin reflux in the pH range of 4–7 took place between 4:00 and 5:40 PM while the patient was upright.

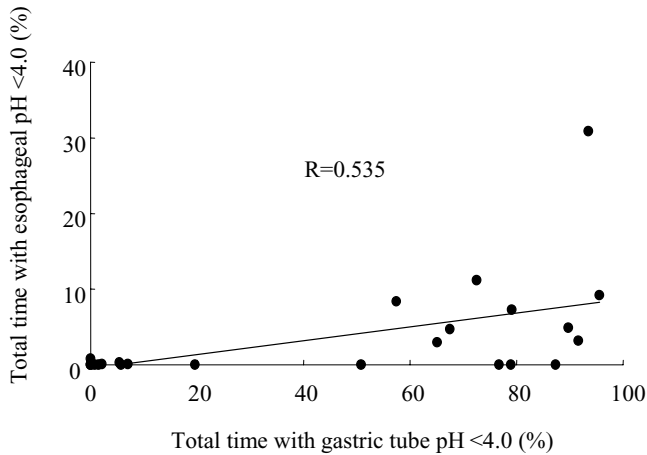


Figure 2. Scattergram showing a significant correlation between the percentages of time during which gastric tube and esophageal pH were below 4.0 ($p < 0.01$).

The mean percentage of time during which esophageal bilirubin absorbance exceeded 0.14 was $5.5 \pm 12.7\%$ (range: 0–55.0%). Elevated DGER was recorded in 11 of 25 patients (44%). The percentage of time during which esophageal bilirubin absorbance exceeded 0.14 in the supine position ($9.3 \pm 23.5\%$; range: 0–94.4%) was significantly greater than that in the upright position ($2.8 \pm 6.8\%$; range: 0–23.5%, $p < 0.03$). Analysis of acid reflux and DGER profile identified four groups: 4 patients (16%) had both elevated acid reflux and DGER (Acid R+/DGER+), 3 (12%) had only elevated acid reflux (Acid R+/DGER–), 7 (28%) had only

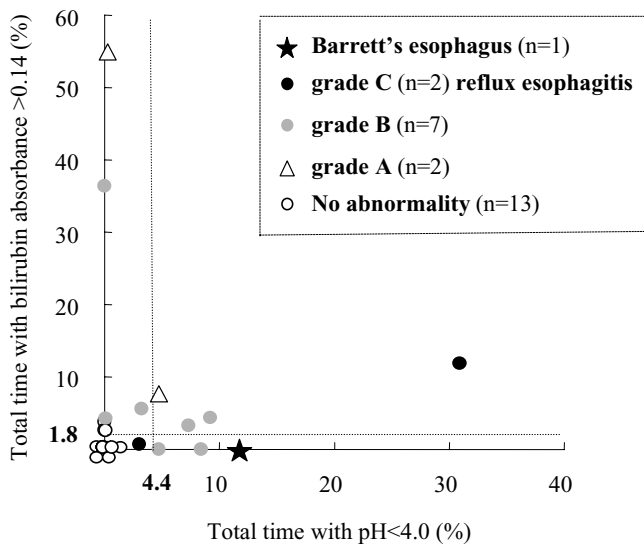


Figure 3. Scattergram showing endoscopic findings, acid reflux, and DGER in each patient. No correlation was evident between percentages of time during which esophageal pH was 4.0 and during which esophageal bilirubin absorbance exceeded 0.14 ($R = 0.02$, $p = 0.925$). Reflux patterns were classified into three groups: both elevated acid reflux and DGER (4 of 14 patients with acid reflux and/or DGER: 29%); only elevated acid reflux (3/14: 21%); and only elevated DGER (7/14: 50%).

Table 1. Relationship between Reflux Symptoms and Acid and/or DGER

Reflux Symptoms	Elevated Acid Reflux and/or DGER		p-Value
	+	–	
+	5	3	0.679
–	8	8	

elevated DGER (Acid R–/DGER+), and 11 (44%) had neither elevated acid nor DGER (Acid R–/DGER–).

Correlations among Reflux Symptoms, Endoscopic Findings, and Acid and/or DGER

Correlations between reflux symptoms and acid reflux or DGER are presented in Table 1. Despite a tendency of increased symptoms in association with elevated DGER, no statistically significant correlation was found between the presence of reflux symptoms and elevated acid reflux and/or DGER ($p = 0.679$). Correlations between endoscopic findings and acid reflux or DGER are presented in Figure 3 and Table 2. A significant correlation was seen between presence of reflux esophagitis or Barrett’s esophagus and elevated acid reflux and/or DGER ($p = 0.001$). On the other hand, no correlation was observed between reflux symptoms and endoscopic esophagitis (Table 3; $p > 0.999$). All 7 patients with elevated acid reflux had reflux esophagitis or Barrett’s esophagus irrespective of DGER. Four of 7 patients with elevated DGER but without elevated acid reflux had reflux esophagitis. The total time during which esophageal pH was below 4.0 in each patient of four was 0%, 0%, 0.3%, and 3.2%.

Moment-to-Moment Comparison of pH and Bilirubin Absorbance

Analysis of simultaneous pH and bilirubin monitoring showed that most esophageal bilirubin exposure occurred in the pH range of 4–7 (Fig. 4). Among total reflux time of

Table 2. Relationship between Endoscopic Findings and Acid and/or DGER

Reflux Esophagitis or Barrett’s Esophagus	Elevated Acid Reflux and/or DGER		p-Value
	+	–	
+	11	1	0.001
–	3	10	

Table 3. Relationship between Reflux Symptoms and Endoscopic Findings

Reflux Esophagitis or Barrett’s Esophagus	Reflux Symptoms		p-Value
	+	–	
+	4	8	>0.999
–	5	8	

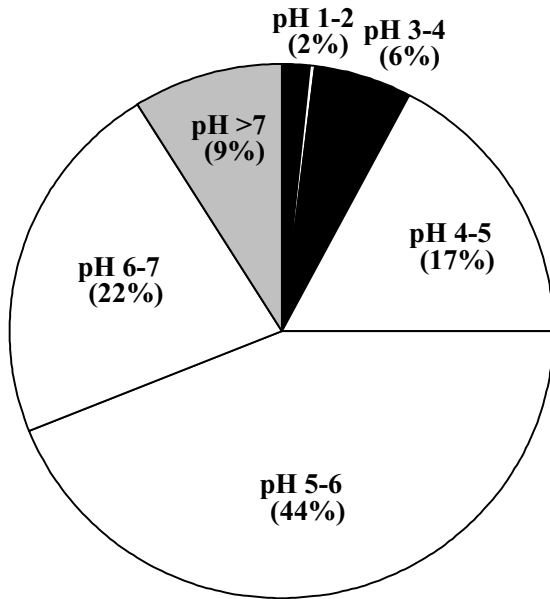


Figure 4. Prevalence of various esophageal luminal pH ranges during the total time showing DGER.

acid or bile, 35% of patients were classified as showing only acid reflux; 5% as acidic bilirubin reflux; and 56% as only bilirubin reflux. Among 5 patients who had acidic bilirubin reflux, 1 showed grade C reflux esophagitis, even though he had no elevation of acid and DGER. The cause of esophagitis in this patient was unexplainable in terms of independent analysis of pH and bilirubin absorbance. However, because this patient had acidic bilirubin reflux during 0.7% of the total monitoring time, the simultaneous acid and bilirubin reflux were suspected to be responsible for the severity (grade C) of reflux esophagitis.

DISCUSSION

In this study, we found no correlation between reflux symptoms and reflux esophagitis. Reflux patterns were classified as showing one of three possibilities: both elevated acid reflux and DGER (29%), only elevated acid reflux (21%), and only elevated DGER (50%). A significant correlation was observed between acid reflux and/or DGER and endoscopic esophagitis. Isolated elevated DGER was confirmed to be a possible cause of reflux esophagitis; this pattern accounted for 28% of reflux in postesophagectomy patients. In most cases the cause of reflux esophagitis could be determined by simultaneous esophageal pH and bilirubin monitoring.

The incidence of reflux symptoms including heartburn and regurgitation after esophagectomy with gastric reconstruction has been reported as 20–67% (5, 7, 9, 16–20). Although reflux symptoms are associated with specific endoscopic findings in gastroesophageal reflux disease patients with an intact stomach (21), no significant relationship was recognized between reflux symptoms and endoscopic findings after esophagectomy in our study and also in another (9). There-

fore, symptoms are not reliable for identifying patients with reflux esophagitis after esophagectomy with gastric reconstruction, when routine endoscopic examination is necessary for detecting reflux esophagitis or Barrett's epithelium.

Incidences of reflux esophagitis and development of Barrett's epithelium after esophagectomy with gastric reconstruction have been reported as 23–72% and 7–48%, respectively (7, 8, 10, 11). Gutschow *et al.* reported that recovery of gastric acidity after esophagectomy leads to esophageal mucosal injury (7), while Öberg *et al.* noticed that columnar metaplasia in the cervical esophagus after esophagectomy was more common in patients having Barrett's esophagus preoperatively (8). Reflux esophagitis and Barrett's esophagus, respectively, were observed in 11 and 1 patients in our study (44% and 4%). Our study included some patients who underwent the study examinations relatively soon after esophagectomy (minimum, 4 months). If the period between esophagectomy and endoscopy had been longer, the severity of esophagitis and incidence of Barrett's esophagus might have been greater.

Our study demonstrated that esophageal acid exposure correlated significantly with gastric tube pH. Acidity in the gastric tube after esophagectomy might be expected to decline following vagotomy and reduction in the fundic gland area. However, some patients still had considerable acidity in the gastric tube, as has been reported elsewhere (Table 4) (7, 8, 16, 17, 23, 24). Acidity in the gastric tube depends on preoperative gastric acidity (24), reduction in the gastric area, and interval after esophagectomy (7). Although 6 patients underwent pH and bilirubin monitoring twice or more during 3 yr in our study, increased gastric acidity with increasing time since the esophagectomy was not observed (data not shown). Among 18 patients with normal esophageal acid exposure, 4 patients (22%) underwent pH monitoring within 6 months after the esophagectomy. Gastric tube acidity in our patients and other Japanese series (23, 24) was lower than in reports from the West (7, 8, 16, 17). This discrepancy might reflect ethnicity-related differences of gastric acid production, differences in gastric construction, and intervals after esophagectomy. Differences in gastric tube acidity are likely reason why esophageal acid exposure in this study was less than in others (Table 4). Another reason for a difference may be differences in location of the esophagogastric anastomosis, since acid reflux after esophagogastric anastomosis in the lower thorax is more common than with anastomosis at the apex of the chest (16, 25). From the viewpoint of postoperative reflux esophagitis, a cervical anastomosis may be superior to an intrathoracic anastomosis (5, 9).

In this study, both esophageal acid and DGER were more common in the supine position, while gastric pH also varied with body position (data not shown). These data are in accord with those of a previous report by Wang *et al.*, who used scintigraphy and pH monitoring (26). Gastric emptying may be a cause of frequent reflux in the supine position, since emptying after esophagectomy depends on position after eating (17, 27). Therefore, patients after esophagectomy should

Table 4. Gastric pH, and Acid Reflux and DGER during Monitoring after Esophagectomy with Gastric Reconstruction in Reports

	Year	Country	Number of Cases	Mean Percentage of Total Time with Gastric pH < 4.0	Mean Percentage of Total Time with Esophageal pH < 4.0	Mean Percentage of Total Time with Esophageal Bilirubin Absorbance Values >0.14 or >0.20
Domergue	1990	France	18	70.9	22.5	—
Bonavina	1992	Italy	16	67.3	11.3	—
Nishikawa	1994	Japan	21	pH < 3: 47.8	—	—
Hashimoto	1995	Japan	41	pH < 3: 39.9	—	—
Gutschow	2001	Belgium	91	pH < 2: 27.3–70.5	—	—
Maier	2001	Austria	18	pH < 3: 74.3	—	—
Öberg	2002	Sweden	32	—	8.0–10.0	>0.20: 0.2–1.3
				pH < 4: 41.9		
This study		Japan	25	pH < 3: 36.9 pH < 2: 30.3	3.4	>0.14: 5.5

sleep in semi-Fowler position (an inclined position obtained by raising the head of the bed about 30 cm). While gastric drainage procedures may facilitate gastric emptying and thus reduce gastroesophageal reflux, they also may promote duodenogastric reflux (28). DGER is affected by the position of the gastric tube. Patients who undergo esophageal reconstruction via a posterior mediastinal route may have more frequent DGER than those who undergo reconstruction via an antesternal or retrosternal route, since after the latter two types of reconstruction the gastric tube is positioned higher than the papilla of Vater when the patient is supine.

Although our definition of elevated acid reflux and DGER was based on data from healthy subjects with an intact stomach, we found a significant correlation between endoscopic findings and acid reflux and/or DGER. Thus, the likely cause of esophagitis after esophagectomy could be determined using these criteria. In our study, reflux patterns after esophagectomy with gastric reconstruction could be classified as showing both elevation of acid reflux and DGER, only elevated acid reflux, or only elevated DGER. The number of patients with bile reflux alone was considerable (28% of study patients). However, when the esophageal pH of patients with elevated DGER is evaluated, buffer effect of duodenal contents should be taken into consideration. The clinical significance of DGER is greater in postesophagectomy patients who underwent gastric drainage procedure than in patients with an intact stomach. Vaezi *et al.* argued that duodenal contents require an acid environment to produce mucosal injury (29). Marshal *et al.* described that esophageal mucosal injury is minimal in patients with isolated bilirubin reflux (30). However, these generalizations might not apply well to patients with gastrectomy or esophagectomy, considering that recent studies and our present one indicated that exposure to duodenal contents alone can cause significant esophageal mucosal injury (31–33).

As presented in this study, simultaneous analysis of pH and bilirubin exposure is useful for determining the cause of reflux esophagitis after esophagectomy. Ambulatory studies of acid and bilirubin reflux have demonstrated that mixed reflux is more harmful than acid reflux alone, suggesting synergistic mechanisms of injury by acid and duodenal contents (15,

22, 34). Moment-to-moment comparison of pH and bilirubin absorbance, which was introduced by Kauer *et al.* (22), is useful for precise analysis of such synergistic action. Our study showed that most esophageal bilirubin exposure occurred within a pH range of 4–7, while 5% of total reflux time of acid or bile among the studied patients was classified as acidic bilirubin reflux. This moment-to-moment analysis should be useful for understanding the cause of esophagitis that might be unexplainable by independent analyses of pH and bilirubin exposure.

In conclusion, patients who underwent Ivor Lewis esophagectomy, intrathoracic esophagogastrectomy, and digital dilation of the pyloric ring frequently had acid reflux and/or DGER, especially in the supine position. Postoperative reflux was closely associated with endoscopically demonstrable esophagitis. Simultaneous 24-h pH and bilirubin monitoring can be helpful in identifying patients at high risk for reflux esophagitis after esophagectomy, studying the effects of esophageal exposure to acid and duodenal juice, and facilitating comparison between reconstruction methods in patients after esophagectomy.

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