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Significance of the Lower Esophageal Sphincter Preservation in Preventing Alkaline Reflux Esophagitis in Patients After Total Gastrectomy Reconstructed by Roux-en-Y for Gastric Cancer

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To clarify the significance of the lower esophageal sphincter (LES) for prevention of alkaline reflux esophagitis (ARE) after total gastrectomy reconstructed by Roux-en-Y (TGRY) for gastric cancer, we investigated LES function and lower esophageal pH in TGRY patients with or without LES preservation. A total of 51 patients 5 years after TGRY were divided into groups A (26 patients without preserved LES) and B (25 patients with preserved LES) and compared with 22 control participants (group C). Manometric study and ambulatory 24-hour esophageal pH monitoring were performed on all patients. Symptomatic and endoscopic AREs in group A were significantly higher than those in group B ($P < 0.05$). The length of LES and maximum LES pressure in group A were significantly shorter and lower, respectively, than in groups B and C ($P < 0.01$). The length of LES and maximum LES pressure in patients with symptomatic ARE were significantly shorter and lower, respectively, than in patients without symptomatic ARE ($P < 0.01$). Percentages of time with pH >7 and pH >8 within 24 hours in group A were significantly higher than those in groups B and C ($P < 0.01$). Preservation of the LES may be necessary to prevent ARE after TGRY.

Key words: Alkaline reflux esophagitis – Total gastrectomy reconstructed by Roux-en-Y – Lower esophageal sphincter – Manometric study – Ambulatory 24-hour esophageal pH monitoring

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Total gastrectomy reconstructed by Roux-en-Y (TGRY) is the global "gold standard" treatment for gastric cancer because it offers a simple procedure and better quality of life.[1,2] The abdominal esophagus, including the lower esophageal sphincter (LES), is excised by the TGRY procedure. Generally, some patients after TGRY experience postgastrectomy syndromes, including alkaline reflux esophagitis (ARE), dumping syndrome, microgastria, and so on.[3–6] After TGRY, patients particularly experience such symptoms of ARE as regurgitation, dysphagia, heartburn, and chest pain.[2,7] Symptoms of ARE are usually more severe in the early postoperative period and improve with time, but they may become permanent about 1 to 2 years after TGRY.[8,9]

The frequency of ARE after TGRY in Japan is approximately 20% to 30% and reduces the patient's quality of life.[6,10,11] ARE after total gastrectomy has been considered to reflect impaired function of the LES.[12–14] In LES preservation, it is functionally important to leave 3 cm or more of the abdominal esophagus from the esophagogastric mucosal junction (EGJ), based on manometric studies.[12,15] However, no convincing evidence has yet been reported regarding the function of LES in patients with symptomatic and/or endoscopic ARE after TGRY for gastric cancer. Ambulatory 24-hour esophageal pH monitoring (A24EPM) is the most reliable method for demonstrating reflux esophagitis.[16–18] To the best of our knowledge, there are no physiologic studies of ARE in patients 5 years after TGRY using both manometric study and A24EPM. We thus studied the LES function using esophageal manometry and the lower esophageal pH using A24EPM in patients with or without preserved LES 5 years after TGRY for gastric cancer.

Patients and Methods

A total of 51 patients who had undergone TGRY for gastric cancer (D2 lymphadenectomy without preserving the vagal nerve) were divided into 2 groups [group A: 26 patients without preserved LES (17 men and 9 women, ages 46–77 years with a mean age of 68.7 years); and group B: 25 patients with preserved LES (17 men and 8 women, ages 45–79 years with a mean age of 66.2 years)] and compared with 22 healthy volunteers who served as controls (group C: 14 men and 8 women, ages 46–78 years with a mean age of 67.5 years). All of the patients in group A had advanced gastric cancer near sited to EGJ. All of the patients in group B had early gastric cancer (submucosal cancer). The present studies were performed on all patients 5 years after TGRY. Postoperative interviews regarding reflux symptoms (bitter taste, heartburn, chest pain, regurgitation, and dysphagia) and endoscopic esophageal reflux findings (Los Angeles classification) for ARE were conducted, and A24EPM was also performed on all patients. None presented local and/or distant tumor recurrence when visiting our hospital during 5 years after their surgery. Neither group had taken medications, such as a gut motility improvement agent and camostat mesilate, at 5 years after TGRY. None of the control participants had symptoms of reflux esophagitis, and none had a history of gastrointestinal symptoms.

Interviews regarding symptoms of ARE and esophageal endoscopy were conducted with all patients before manometric study and A24EPM.

Informed consent was obtained from all individuals participating in the present study. The present study was approved by the ethics committee of Nihon University School of Medicine (Tokyo, Japan).

Manometric study

Esophageal manometry was performed by the low-compliance infused open-tip method. The length of LES (LLES) and maximum LES pressure (MLESP) were measured with a catheter [a 1-m polyethylene tube (outer diameter, 1.8 mm; internal diameter, 1 mm) with a side hole (diameter, 0.5 mm)]. The catheter was connected to a transducer (model YHP 1280C, Hewlett-Packard, Tokyo, Japan) and to a polygraph (thermal tip recorder model 8805, Hewlett-Packard, Tokyo, Japan). Distilled water was infused at a constant rate of 0.5 mL/min, produced by nitrogen gas pressure and an Arndorfer internal pressure measurement system (Pneumohydraulic capillary system, Arndorfer, Milwaukee, Wisconsin). The catheter was inserted into the stomach via the nose. The station pull-through method was used and measurements were made in the abdominal esophagus from the stomach. The apparatus used in the present study was specially designed for testing and recording the pressure of the LES. Without administration of a sedative, esophageal manometry was performed at 8 AM with the participants in the left lateral decubitus position with knees drawn up.

The measurement method of the LLES and MLESP was the following. A catheter was pulled out from the upper stomach to the abdominal esophagus including LES by station pull-through

method. The high-pressure zone was obtained in this process. The LES has a higher basal or resting pressure than either the esophagus above or the stomach below. We measured the LLES from the start point of a high-pressure zone (the lower margin of the LES) to the end point of a high-pressure zone (the upper margin of the LES). The highest-pressure value of the high-pressure zone was measured as the MLESP.

Method of A24EPM

The present study used a pH probe made using monocrystant antimony hydrogen electrodes (Synetics Medical, Stockholm, Sweden) mounted on a polyvinyl catheter (outside diameter, 2.1 mm). The pH probe was connected to a portable digital sampling unit in order to record the pH readings (Digitrapper KK II Gold, Synectics Medical). The pH probe was calibrated in a standard buffer solution at a pH of 7 and a pH of 1 before and after monitoring. The pH probe was passed transnasally and was positioned 5 cm above the upper border of the EGJ, as measured by manometry (see Chen and Wang[17]). Continuous pH measurements were recorded for 24 hours. At the completion of each study, the data were offloaded to an ALR PowerFlex computer (Advanced Logic Research-Irvine, Los Angeles, California) for data analysis using the EsopHogram/Gastrop-graH program (Synectics Medical).

The patients were encouraged to consume their normal diet during pH measurements. Apart from abstaining from alcohol and tobacco, there were no other restrictions on the timing, frequency, and content of meals. They were also advised to work and sleep in their normal patterns. All study participants kept a diary of events such as meals, supine episodes, drug intake, and usual events. Drugs that influence alimentary tract motility were to be avoided for 1 week before the manometric study and A24EPM. In A24EPM, we measured 24 hours % of time with pH >7 and pH >8 (percentage of time with pH >7 and pH >8 within 24 hours). A24EPM was started after the manometric study.

Indication of TGRY with preserving LES

In early gastric cancer (mucosal and submucosal cancer), there is a distance of 2 cm or more between the EGJ and the oral side of the tumor edge. In advanced gastric cancer, this distance is 4 cm or more. D1 lymph node resection preserving the vagal nerves was selected in cases of mucosal cancer, and D2 lymph node resection without preserving the vagal nerves was chosen in the other cases.

We previously suggested, based on histology, that cancer cell invasion of the gastric wall 2 cm or less from the oral side of the tumor edge represents early gastric cancer, whereas 4 cm or less from the oral side of the tumor edge is advanced gastric cancer.[5,11]

Severing of abdominal esophagus to preserve LES

In complete LES preservation, it is functionally important to preserve the abdominal esophagus for 3 cm or more from the EGJ.[7,19] The EGJ is identical to the lower part of the abdominal esophagus (*i.e.*, LES). Therefore, the authors preserved the esophagus at the His angle at a left angle to the longitudinal axis of the esophagus (Fig. 1). To determine the position to cut the esophagus, the region was also confirmed on preoperative measurements of esophageal pressure, measuring the length from the stomach to the pressure-increase region in the abdominal esophagus by esophageal manometry. When the EGJ could not be clearly identified, the region was confirmed by gastrotomy. Reflux-prevention methods, such as the Nissen method, were not necessary to support the present technique for LES preservation.[9,20] See Tomita *et al*[11] for the detailed operative technique of preserved LES. Figure 2 is an illustration of completed TGRY with preserved LES.

Statistical analysis

Results are presented as the mean ± SD. Data were analyzed using nonparametric Kruskal-Wallis test

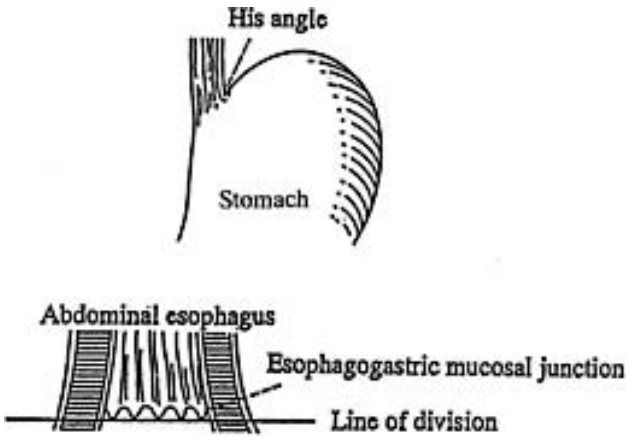

Fig. 1 Technique of preservation of the LES. LES preservation is performed while leaving the abdominal esophagus from the EGJ. The EGJ is located at the His angle.

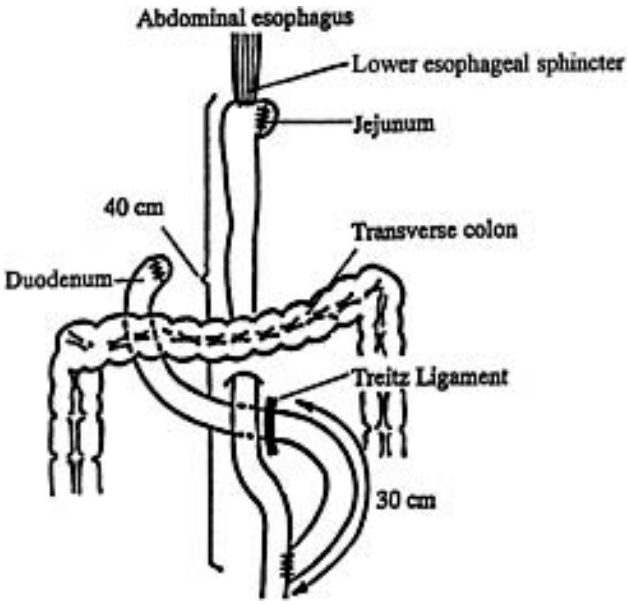

Fig. 2 An illustration of completed total gastrectomy reconstructed by Roux-en-Y with preserved LES. This operation creates a 40-cm segment of jejunum between the esophagojejunostomy and jejuno-jejunostomy.

with Bonferroni correction, and frequency rates of both symptoms and endoscopic findings of ARE were compared using the χ^2 test. A P value less than 0.05 was considered statistically significant.

Results

Characteristics of patients

There were no significant differences in characteristics of patients after TGRY with or without preserved LES (Table 1).

Characteristics of ARE

Symptoms of ARE

Symptoms of ARE (*i.e.*, bitter taste, chest pain, heartburn, regurgitation, and dysphagia) were noted in 30.8% (8 of 26) of group A and 8.0% (2 of 25) of group B. In addition, there were significant differences between groups A and B ($P < 0.05$; Table 2).

Endoscopic ARE

Endoscopic ARE was noted in 19.2% (5 of 26) of group A and 0% (0 of 25) of group B. There was a significant difference between groups A and B ($P < 0.05$; Table 2).

According to these results, group A showed higher rates of symptomatic and endoscopic ARE compared with group B. Endoscopic ARE was only found in group A. According to the Los Angeles classification, 3 patients were grade A and 2 patients were grade B.

Table 1 Characteristics of patients after TGRY with or without preserved LES

	Group A	Group B	*P*
Patients, No.	26	25	ns
Men/women, No.	17/9	17/8	ns
Age, y	46–77 (average, 68.7)	45–79 (average, 66.2)	ns
TNM classification, No.			
Stage IA	10	13	ns
Stage IB	6	5	ns
Stage IIA	4	3	ns
Stage IIB	3	2	ns
Stage IIIA	3	2	ns
Postoperative complication	None	None	
Medication	None	None	
Recurrence	None	None	

ns, not significant.

Manometric parameters

Length of the LES

LLESs in groups A, B, and C were 1.9 ± 0.5, 3.3 ± 0.6, and 4.1 ± 0.5 cm, respectively. In addition, LLES in group A was significantly shorter than those in groups B and C ($P < 0.01$, respectively). LLES in group B was significantly shorter than that in group C ($P < 0.01$). LLESs were 1.8 ± 0.4 cm in patients after TGRY with symptomatic ARE and 3.4 ± 0.5 cm in patients after TGRY without symptomatic ARE. In addition, there was a significant difference between patients after TGRY with symptomatic ARE and patients after TGRY without symptomatic ARE ($P < 0.01$; Table 3).

Table 2 Alkaline reflux esophagitis

	Group A (n = 26)	Group B (n = 25)
Symptoms of ARE, % (No.)		
Positive	30.8 (8/26)[a]	8.0 (2/25)[b]
Negative	69.2 (18/26)	92.0 (23/25)
Endoscopic ARE, % (No.)		
Positive	19.2 (5/26)[c]	0 (0/25)[d]
Los Angeles classification		
Grade A, No.	3	0
Grade B, No.	2	0
Grade C, No.	0	0
Grade D, No.	0	0
Negative, % (No.)	80.8 (21/26)	100 (25/25)

[a] versus [b]: $P < 0.05$; [c] versus [d]: $P < 0.05$.

Table 3 Manometric parameters of LES

	Group A (n = 26)	Group B (n = 25)	Group C (n = 22)	Patients with symptomatic ARE (n = 10)	Patients without symptomatic ARE (n = 41)
Length of LES, cm	1.9 ± 0.5[a]	3.3 ± 0.6[b]	4.1 ± 0.5[c]	1.8 ± 0.4[g]	3.4 ± 0.5[h]
Maximum LES pressure, mmHg	6.6 ± 2.9[d]	16.1 ± 3.8[e]	24.9 ± 7.3[f]	6.4 ± 3.1[i]	17.3 ± 3.6[j]

[a] versus [b]: $P < 0.01$; [a] versus [c]: $P < 0.01$; [b] versus [c]: $P < 0.01$.
[d] versus [e]: $P < 0.01$; [d] versus [f]: $P < 0.01$; [e] versus [f]: $P < 0.01$.
[g] versus [h]: $P < 0.01$; [i] versus [j]: $P < 0.01$.

Maximum LES pressure

MLESPs in groups A, B, and C were 6.6 ± 2.9, 16.1 ± 3.8, and 24.9 ± 7.3 mmHg, respectively. In addition, MLESP in group A was significantly lower than those in groups B and C ($P < 0.01$, respectively). MLESP in group B was significantly lower than that in group C ($P < 0.01$). MLESPs were 6.4 ± 3.1 mmHg in patients after TGRY with symptomatic ARE and 17.3 ± 3.6 mmHg in patients after TGRY without symptomatic ARE. In addition, there was a significant difference between patients after TGRY with symptomatic ARE and patients after TGRY without symptomatic ARE ($P < 0.01$; Table 3).

Group A showed an impaired function of the LES compared with groups B and C. Patients after TGRY with symptomatic ARE also showed an impaired function of the LES compared with patients after TGRY without symptomatic ARE.

A24EPM

Twenty-four–hour % time pH >7

Twenty-four–hour % time pH >7 in groups A, B, and C was 61.9% ± 9.6%, 29.1% ± 13.2%, and 4.9% ± 1.8%, respectively. In addition, the 24-hour % time pH >7 in group A was significantly higher than those in groups B and C ($P < 0.01$, respectively). The 24-hour % time pH >7 in group B was also significantly higher than that in group C ($P < 0.01$; Table 4). All patients with symptomatic ARE showed 24-hour % time pH >7.

Twenty-four–hour % time pH >8

The 24-hour % time pH >8 in groups A, B, and C was 14.2% ± 5.4%, 2.7% ± 1.1%, and 2.1% ± 0.4%, respectively. In addition, the 24-hour % time pH >8 in group A was significantly higher than those in groups B and C ($P < 0.01$, respectively). There was no significant difference between groups B and C (Table 4). All patients with endoscopic ARE showed 24-hour % time pH >8.

The 24-hour % time pH >7 patients after TGRY without preserved LES was significantly higher than that in patients after TGRY with preserved LES. All patients with symptomatic ARE showed 24-hour % time pH >7. The frequencies of 24-hour % time pH >8 in patients after TGRY without preserved LES were also significantly higher than those in patients after TGRY with preserved LES.

Discussion

TGRY without preserving LES for gastric cancer has been widely employed as a standard technique worldwide. However, approximately 20% to 50% of patients (symptomatic ARE, 30%∼50%; endoscopic ARE, 5%∼30%) after TGRY without preserving LES experience ARE and are troubled by ARE in the long term after surgery.[8,12,21–24] Symptoms of ARE (bitter taste, heartburn, chest pain, regurgitation, and dysphagia)—that is, symptomatic ARE—are usually more severe in the early postoperative period and improve with time, but they may become permanent about 1 to 2 years after surgery.[5,8,9,20,21] However, there is no study on ARE 5 years after TGRY. Therefore, we performed the present studies in patients 5 years after TGRY for gastric cancer.

In clinic, ARE is classified into 2 types: symptomatic ARE and endoscopic ARE.[6,12] It is considered that symptomatic ARE is caused by the regurgitation of duodenal contents, such as bile acid, pancreatic juice, and duodenal juice, into the esophagus and/or functional dysmotility of the esophagus, including the LES.[6,12,23] Upper digestive endoscopy is the "gold standard" to detect ARE (endoscopic ARE) after gastric surgery.[21] According to the Los Angeles classification, esophagitis lesions are classified into 4 types: grade A, one or more mucosal breaks no longer than 5 mm; grade B, one or more mucosal breaks longer than 5 mm, none of which extend between the tops of 2 mucosal folds; grade C, at least one mucosal break that extends between the tops of 2 or more mucosal folds and

Table 4 Twenty-four–hour % time pH >7 and pH >8

	Group A (n = 26)	Group B (n = 25)	Group C (n = 22)
24-hour % of time for pH >7	61.9 ± 9.6[a]	29.1 ± 13.2[b]	4.9 ± 1.8[c]
24-hour % of time for pH >8	14.2 ± 5.4[d]	2.7 ± 1.1[e]	2.1 ± 0.4[f]

[a] versus [b]: $P < 0.01$; [a] versus [c]: $P < 0.01$; [b] versus [c]: $P < 0.01$.

[d] versus [e]: $P < 0.01$; [d] versus [f]: $P < 0.01$; [e] versus [f]: not significant.

involves less than 75% of the esophageal circumference; and grade D, mucosal breaks that involve at least 75% of the esophageal circumference.[19] Generally, endoscopic ARE shows grade A or B in patients after conventional TGRY.[21] In this study, symptomatic AREs were significantly more frequently noted in patients after TGRY without preserved LES than in those with preserved LES. Endoscopic ARE was only found in TGRY without preserved LES. All patients with endoscopic ARE also had symptomatic ARE. According to the Los Angeles classification, 3 patients were grade A and 2 patients were grade B.

It is well known that ARE frequently occurs when a short segment of the jejunum, less than 30 cm, is left between the esophagojejunostomy and jejunojejunostomy. Therefore, to prevent ARE, Roux-en-Y anastomosis after total gastrectomy has been made using a long segment of jejunum (length, 40∼60 cm).[22–24] Our patients had a 40-cm segment of jejunum between the esophagojejunostomy and jejunojejunostomy. However, ARE could not be prevented by a 40-cm segment of jejunum after conventional TGRY without preserved LES.[5,9,20] It is reported that reconstruction operations preserving the abdominal esophagus including LES as much as possible are appropriate to prevent ARE in patients after total gastrectomy, including TGRY.[5,9,20,25,26] We thus studied the LES function in patients with or without preserved LES 5 years after TGRY for gastric cancer.

The LES is a specialized structure of the distal part of the esophagus at the junction of the esophagus and the stomach.[25,26] Anatomically, it is a dynamic sphincter that is indistinguishable from other circular muscles in the esophagus.[25] However, the LES is clearly recognizable manometrically.[25–27] At rest, the LES plays an important role in preventing gastrointestinal reflux by maintaining an intraluminal pressure, higher than the stomach pressure.[25,26] The LES relaxes upon swallowing and allows the passage of ingested food and liquids into the stomach and substitute stomach.[25] The intrinsic resting tone of the LES is an important factor in the prevention of reflux and is characterized manometrically as a 3-cm zone of specialized muscle from the EGJ that maintains a tonic activity.[28,29] That is to say, it is necessary for the surgeon to preserve the abdominal esophagus completely. In the present manometric study, the LLES in patients after TGRY without preserved LES was significantly shorter than that in patients after TGRY with preserved LES. The MLESP in patients after TGRY without preserved LES was significantly lower than that in patients after TGRY with preserved LES. The LLES and MLESP in patients with symptomatic ARE were significantly shorter and lower, respectively, than those in patients without symptomatic ARE. Patients after TGRY without preserved LES showed an impaired function of the LES compared with patients after TGRY with preserved LES and control participants. Patients after TGRY with symptomatic ARE also showed an impaired function of the LES compared with patients after TGRY without symptomatic ARE. Previously, we reported the manometric study in patients with or without preserved LES 2 years or more (*i.e.*, range, 25–34 months) after TGRY for gastric cancer.[30] In the present studies, we obtained an improvement of the MLESP in patients with preserved LES 5 years (*i.e.*, 60 months) after TGRY (16.1 ± 3.8 mmHg) compared with that in patients with preserved LES 2 years or more after TGRY (11.3 ± 2.5 mmHg). However, there was no difference in the LLES values among them (the former, 6.6 ± 2.9 mmHg; the latter, 6.5 ± 3.2 mmHg). In accordance with these data, the MLESP function in patients with preserved LES 5 years after TGRY may improve compared with that in patients with preserved LES 2 years or more after TGRY.

The A24EPM is the most reliable method for demonstrating gastroesophageal acid reflux and/or alkaline reflux.[18,31] Jamieson *et al*[31] also concluded that computerized A24EPM in the outpatient setting provides accurate and reproducible results. Previous studies have shown that severe endoscopic ARE after gastric surgery is indicated when the 24-hour % time is pH >8.[14] Both symptomatic and endoscopic AREs were also found in patients with 24-hour % time pH >7.[16] It is conventionally agreed that the pH sensor should be positioned 5 cm above

the upper margin of the EGJ, and this location is usually determined by prior esophageal manometry.[18] We therefore placed the sensor at 5 cm above the EGJ and performed 24-hour % time pH >7 and pH >8. In the present studies, the 24-hour % time pH >7 in patients after TGRY without preserved LES was significantly higher than that in patients after TGRY with preserved LES. All patients with symptomatic ARE showed 24-hour % time pH >7. The frequencies of 24-hour % time pH >8 in patients after TGRY without preserved LES were also significantly higher than those in patients after TGRY with preserved LES. All patients with endoscopic ARE showed 24-hour % time pH >8. According to both the manometric study and A24EPM results, the ARE after TGRY without preserved LES may be due to impairment of the LES function.

In conclusion, symptomatic AREs were significantly more frequent in TGRY patients without preserved LES compared with those with preserved LES. Endoscopic ARE was only found in patients without LES. Both 24-hour % times pH >7 and pH >8 in TGRY patients without preserved LES were significantly higher than those in TGRY patients with preserved LES and healthy participants. Endoscopic ARE can only be prevented in patients after TGRY with preserved LES. According to the present studies, preservation of the LES may be necessary to prevent ARE after TGRY.

As a symptomatic evaluation, it was insufficient only by hearing about presence or absence by an interview. Detailed analysis of symptomatic evaluation will be required in the future. The pathogenesis of AER is multifarious, and different mechanisms may be involved in different patients.[24] In addition, abnormal esophageal peristalsis may be involved in the LES dysfunction observed in patients with esophagitis.[27] Thus, further assessment of the relationships between esophageal motility including LES and esophageal pH monitoring will be required in the future.

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