

Gastroesophageal reflux after per-oral endoscopic myotomy: what should we know?

Running Title: Gastroesophageal reflux after per-oral endoscopic myotomy

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ABSTRACT

Achalasia is a primary esophageal motility disorder, characterized by the distal motility disorder with high-level pressure in the lower esophageal sphincter (LES). Nowadays, POEM, as a novel endoscopic technology, has been accepted by the majority of patients with achalasia. The efficacy of POEM is evident in most studies; however, most researchers have found that the occurrence of gastroesophageal reflux (GER) after POEM is also much higher than other two therapies. The reasons for post-POEM GER mainly includes destroying the structure of LES, abnormal peristalsis of esophageal body and without a fundoplication as Heller surgery. In addition, the sensitivity and specificity to diagnose GER through symptom are lower, we need a comprehensive analysis of symptom, endoscopy and 24-hour pH monitoring. The endoscopy has its

unique advantages in biopsy for early detection of esophageal cancer. 24-hour pH testing can distinguish between reflux and food fermentation. For patients with refractory GER, genotype cytochrome P450 2C19 variability may be the cause of them. Therefore, for those patients, they can use PPIs with less affected by CYP2C19 and think about the option of therapeutic endoscopy.

Key words: achalasia, per-oral endoscopic myotomy, gastroesophageal reflux

Achalasia is a primary esophageal motility disorder with an incidence of about 1.6-2/100 000.^[1, 2] There is no evident difference in the occurrence of achalasia by sex or race. Majority of patients are diagnosed with age of 30 - 60.^[3] As achalasia is an motility disorder of esophagus, the gold standard is high-resolution esophageal manometry (HREM). According to Chicago classification version 4.0, Achalasia can be divided into three types: Type I achalasia: Abnormal median integrated relaxation pressure (IRP) and 100% failed peristalsis; Type II achalasia: Abnormal median IRP, 100% failed peristalsis, and $\geq 20\%$ swallows with pan esophageal pressurization; Type III achalasia: Abnormal median IRP and $\geq 20\%$ swallows with premature/spastic contraction and no evidence of peristalsis.^[4]

Achalasia mainly has three non-drug therapies, including peroral endoscopic myotomy (POEM), laparoscopic Heller surgery, and pneumatic dilation (PD). POEM has been reported since 2010, and intended to be the preferred treatment for achalasia due to its advantages of minimally invasive surgery and good efficacy.

The long-term complications after POEM are widely concerned among experts and physicians. Gastroesophageal reflux (GER) after POEM has been carried out extensive research into its epidemiology, reasons, predictors, diagnosis, prevention and treatment of post-POEM GER. In this review, we will state recent studies related to post-POEM GER and summarize the advances in GER after POEM.

EPIDEMIOLOGY OF GER AMONG POEM, PNEUMATIC DILATATION AND HELLER SURGERY

The treatment approaches of achalasia mainly include POEM, laparoscopic Heller's myotomy (LHM) and pneumatic dilatation (PD). Many studies have proved that post-POEM GER is more frequent than other two surgeries.

A latest meta-analysis of GER after Heller surgery revealed that approximately 8.8% of patients had postoperative gastroesophageal reflux symptoms, 16.8% had abnormal acid exposure time (AET), and 7.6% were diagnosed with reflux esophagitis.^[5] Results of several clinical trials and meta-analyses have shown that 8.5-18.5% of patients after POEM have symptoms of GER characterized by acid reflux and heartburn, 13%-23.2% of patients have a diagnosis of reflux esophagitis in endoscopic view, and approximately 47%-57.8% of patients have abnormal results on pH monitoring.^[6] A recent multicenter, randomized trial compared POEM with laparoscopic Heller's myotomy has shown that reflux esophagitis has a higher occurrence in the patients after POEM rather than LHM at 2 years follow-up (44% vs. 29%; odds ratio, 2.00; 95% CI, 1.03 to 3.85).^[7] Therefore, many studies and researches have noticed that POEM has a higher rate in GER after surgery than Heller and have strong evidence.

Besides LHM, pneumatic dilation is a common therapy for achalasia especially for patients with prior treatment or intolerance of operation. There are few studies about comparison of GER after between PD and POEM. In a clinical randomized study, Ponds et al have compared gastroesophageal reflux after POEM and PD, and the rate of esophagitis is much higher in POEM (41% vs 7%, $P = 0.002$).^[8] However, the time with esophageal pH < 4 during pH-impedance monitoring was similar between the POEM vs the PD at the one year (7.0% vs 3.0%, $P = 0.95$). A systematic review and Bayesian network meta-analysis, studying PD, POEM and Heller, shows that there is no difference between PD group and Heller group in gastroesophageal reflux after surgery, while POEM is higher than others.^[9]

REASONS FOR HIGHER RATE OF POST-POEM REFLUX

The main cause is that POEM is an operation to relieve the symptoms of achalasia by

building a submucosal tunnel and cutting esophageal muscle layer, which destroys the structure of lower esophageal sphincter (LES) and reduces the pressure. A statement for GER after POEM in Japan has suggested muscle incision of more than 4 cm and incision of the sling fibers in the gastric side is related to reflux esophagitis^[10]. A single-institutional retrospective study reported that IRP was very significantly decreased at one-year follow-up after POEM (pre-POEM 28 ± 12 mmHg vs. post-POEM 11 ± 4 mmHg, $P < 0.001$), which destroyed LES pressure to induce GER.^[11]

Besides that, Achalasia has its own esophageal motility characteristics. A case-control study comparing GER between achalasia and non-achalasia patients shows a significant difference between them. One possible reason is abnormal peristalsis of esophageal body in achalasia, which may affect the clearance rate of esophageal acid after POEM.^[12] This was also confirmed by other studies. A retrospective study was conducted with 237 patients undergoing POEM and suggested that about 28.7% patients had some signs of contractile activity in HRM and 22.0% of patients founded contractions.^[13] Another analysis of a prospective database including 23 patients showed that only 60.8% of patients have founded partial recovery of esophageal body peristalsis and it was significantly related to short symptomatic duration (< 12 months) before POEM ($P = 0.012$).^[14] However, achalasia is a long-term disease with an end-stage of sigmoid-type achalasia. This study observed that it is absence of peristalsis in all sigmoid-type achalasia patients, who has long duration of symptom, before and after POEM in a retrospective analysis. Therefore, POEM has limited effect on improving esophageal peristalsis in patients with achalasia, which has more instances of reflux.^[15]

PREDICTORS FOR GER AFTER POEM

Prediction of GER after POEM is the main focus of the studies to identify patients with risk factors and develop an appropriate therapeutic strategy. Predictors can be classified into three parts according to before, during and after POEM, as summarized in Figure 1.

Baseline data of achalasia patients influence the occurrence of GER after POEM. A

systematic review, which contained 17 studies about POEM, showed that the incidence of GER after POEM seemed to be much higher in non-Asian researches (Asian 16.0% vs. non-Asian 22.8%). Similar to gastroesophageal reflux disease (GERD), it is founded that post-POEM GER is associated with increasing body mass index (BMI) .^[16-18] A study has shown that women are a risk factor of post-POEM GER.^[19] In a retrospective study by Arevalo, G et al, the higher preoperative Eckardt score in HRM was correlated in reflux esophagitis used by endoscopy post-POEM.^[20]

Some studies also investigated the relationship between postoperative GER and the factors related to POEM procedure. Sling muscle fibers is an important part of the lower esophageal sphincter to maintain LES high pressure and prevent gastroesophageal reflux. The direction and depth of myotomy were fully discussed for their effect on GER after POEM in different studies. POEM has anterior and posterior myotomy according to the direction of submucosal tunnel. Compared with anterior myotomy, posterior myotomy damages fibers and increases the risk of injury, leading to an increased incidence of GER. However, many studies have found that anterior and posterior myotomy have little effect on postoperative POEM reflux. Recent clinical studies on anterior and posterior myotomy are summarized in Table 1. Among them, Ramchandani et al. conducted a clinical trial that founded an apparent increase in AET during 24h pH monitoring in patients in posterior myotomy ($2.98\% \pm 4.24$ vs $13.99\% \pm 14.48$; $P < 0.01$) .^[21] However, other randomized trials in Table 1 and two recent meta-analyses showed no statistical difference in postoperative GER between anterior and posterior myotomy group.^[22, 23] Therefore, majority of studies show that the direction of myotomy has no significant correlation with GER after POEM. POEM can also be classified into full-thickness myotomy (FTM) and circular muscle myotomy according to the depth of muscle incision. As for the relationship between the depth of myotomy and GER, a multivariate analysis of a study showed that full-thickness myotomy (FTM) was relevant to GER after POEM.^[24] However, some clinical trials have come to the opposite conclusion, and a recent systematic review and meta-analysis also suggested that the depth of POEM myotomy has no statistical difference in postoperative reflux, so we need more studies to verify it.^[22, 25, 26]

In addition, achalasia also has unique dynamic characteristics after POEM. Some studies show that lower IRP is correlated with postoperative GER.^[6, 27] In retrospective research in China, it was observed that the post-POEM upper esophageal sphincter pressure (UESP) was significantly higher in the post-POEM GER group than the non-reflux patients ($P = 0.042$).^[28] The functional lumen imaging probe (FLIP), which is thought as a novel technology, applies impedance planimetry to evaluate esophageal morphology in real time. A study about using FLIP before and after POEM has found that a final cross-sectional area $> 96 \text{ mm}^2$ was a predictor of post-POEM reflux at 2 years of follow-up.^[29]

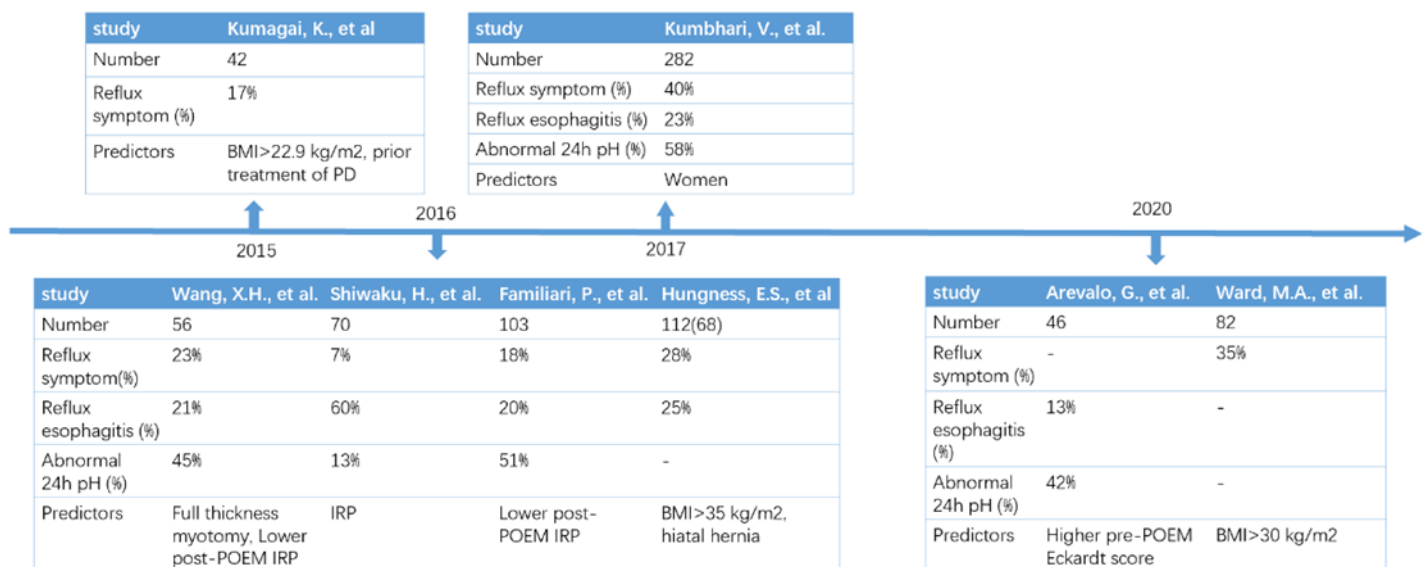


Figure 1 Studies about predictors for post-POEM GER in different years

BMI: body mass index; PD: pneumatic dilatation; IRP: integrated relaxation pressure; POEM: Per-oral endoscopic myotomy

Table 1 GER after POEM in randomized trials comparing anterior with posterior myotomy

Study	Number of cases	GERDQ score or GER symptom (%)	Reflux or esophagitis (%)	Abnormal 24-hour pH (%)	Conclusion
Ramchandani, M., et al. ^[21]	Anterior myotomy 30 Posterior myotomy 30	- - -	24.0% 33.3%	2.98% ± 4.24% 13.99% ± 14.48%	Esophageal acid exposure was significantly increased in posterior myotomy group (P<0.01)
Khashab, M.A., et al. ^[30]	Anterior myotomy 73 Posterior myotomy 77	6 (GERDQ) 6 (GERDQ) -	- -	49.15% 41.67%	No statistical difference between two groups (P>0.05)
Ichkhanian, Y., et al. ^[31]	Anterior myotomy 54 Posterior myotomy 57	6 (GERDQ) 6 (GERDQ) -	- -	- -	No statistical difference between two groups (P=0.08)
Tan, Y., et al. ^[32]	Anterior myotomy 31 Posterior myotomy 32	20.0% 16.7% -	16.7% 16.7%	26.70% 33.30%	No statistical difference between two groups (P>0.05)

GERDQ: gastroesophageal reflux disease questionnaire; GER: Gastroesophageal reflux.

THE DIAGNOSIS OF POST-POEM GER

The methods to diagnose post-POEM GER mainly include symptom evaluation, gastroscopy and 24-hour pH testing, among which the 24-hour pH monitoring has the highest sensitivity. However, postoperative gastroesophageal reflux of POEM has an incidence ranging from 8.5% to 57.8%. According to different examination methods, the incidence of GER after POEM varies. The Lyon Consensus 2018 published the latest diagnostic criteria for GERD: AET is an indicator to identify gastroesophageal reflux in 24-hour pH testing as known by time pH <4 during the whole inspection time. Conclusive evidence for GERD in the consensus is LA grade C or D esophagitis, Barrett's esophagus, peptic stricture and AET>6%.^[33] However, gastroesophageal reflux after POEM is different from GERD due to its motility characteristics, diagnosis of post-POEM GER inclines to comprehensive assessment.

Symptom assessment

Questionnaire evaluation is a common method to evaluate patients' GER in clinical practice. It is widely used in symptomatic assessment because of its advantages of simplicity and convenience. The gastroesophageal reflux disease questionnaire (GERDQ) is widely used, but some studies have shown that there is a sensitivity of 62%-66% and specificity of 64%-67% for the assessment of GERD.^[34] The sensitivity by assessing symptoms to diagnose postoperative reflux is low, because previous studies have also found that over than half of patients show asymptomatic reflux after POEM^[20]. In addition, reflux symptoms after POEM can be caused by many reasons, including real reflux, fermentation process of food in the esophagus and esophageal hypersensitivity.^[35] A case-control study included 40 treated achalasia patients and half of them with symptoms of GER. It shows that it is no significantly difference in AET whether patients have symptoms or not. However, patients with reflux symptoms are hypersensitive to acid (RS+: 4 vs RS-:30 min, $P<0.001$) in acid perfusion test and have higher acid fermentation (RS-: 1.8% vs, RS+: 6.6% $P=0.03$).^[36] Therefore, 24-hour

pH testing and acid perfusion test are necessary for patients with symptoms of GER after POEM.

Endoscopy

Endoscopy is one of the common medical examinations to assess gastroesophageal reflux. As is known in Lyon consensus, the evidence of GERD under endoscopy included reflux esophagitis, esophageal stricture and Barrett's esophagus.^[33] Endoscopy is a useful tool to find the above lesions. Some studies have shown that erosive esophagitis only can be founded in 30% of patients with GER symptoms, and only 6.7% of achalasia receiving proton pump inhibitors (PPIs) are diagnosed as esophagitis under endoscopy^[37]. The consensus of experts in China suggests that patients with achalasia should be examined at 3, 6, 12 months after treatment, while clinical practice guidelines in Japan suggests that patients with achalasia should be underwent gastroscopy at 2 to 3 months after POEM.^[38] If it is no abnormality in endoscopy, patients can be followed up once a year thereafter. Besides that, achalasia is a risk factor proven by several studies for esophageal cancer. A review discussing the association of achalasia and esophageal cancer shows that it is about 50 times of esophageal squamous cell carcinoma in achalasia than the general population.^[39] Therefore, regular gastroscopy and biopsy for pathological staining are effective methods for early detection of esophageal cancer. Currently, the incidence of esophageal carcinoma after POEM for achalasia is unclear and lack of relevant studies.

24-hour pH monitoring

24-hour pH monitoring allows real-time monitoring of the duration or onset of esophageal acid exposure and quantitative measurement of reflux. Multichannel intraluminal impedance-pH monitoring (MII-pH) is a novel approach that not only determines the direction of movement of food, but also can monitor reflux of liquid, gas, or solid and measure accurate pH of reflux.^[40] Multichannel intraluminal impedance-pH monitoring has a higher sensitivity of 87.42% for GERD, which is more accurate than conventional pH monitoring and is less affected by proton pump inhibitors (PPIs) therapy.^[41] Unlike other diseases, due to its motility disorder, false positives are likely to result in achalasia patients. A study has found that there are two

types of AET elevation during 24-hour pH monitoring: 1) pH <3 and sharp decline with slow clearance, which is typical of GER; 2) the pH rarely falls below 3.7 and slowly decreases, which is the fermentation process of food is stagnated in the esophagus.^[42] Fermentation process of food is quite common in achalasia before and after treatment. In achalasia after treatment, over half of the patients with abnormal AET may be due to fermentation.^[42] We should notice that there is totally different in therapeutic strategy between GER and food fermentation. Food fermentation may mean that esophageal emptying is severely damaged and need timed barium esophagogram to assess the effect of POEM and determine whether additional surgery is needed. Therefore, some studies recommend that pH<3 should be taken as the recommended standard for 24-hour pH testing of GER among patients with achalasia, and the possibility of false GER caused by food fermentation should be excluded through manual review.^[43]

PREVENTION AND TREATMENT OF GASTROESOPHAGEAL REFLUX AFTER POEM

Drug therapies

The drug therapy of GER after POEM mainly consists of acid suppressive drugs as PPIs. A number of studies were conducted to study the alleviating effect of PPI drugs on GER after POEM. Hernandez et al. founded that the rate of postoperative gastroesophageal reflux is about 55% during the 1-year follow-up period for patients after POEM, while the rate decreased to 3% after 5 years of PPIs use.^[44] The meta-analysis of Repici et al. shows that the using rate of PPIs after POEM is higher, ranging from 2.6% to 27.8%.^[5] A large, single-center study included 209 patients after POEM found that PPIs therapy is effective in most patients with erosive esophagitis in the majority of patients (81.4 %).^[45] Therefore, many trials proved that PPIs therapy can control patients' symptoms well, and most patients are responded to PPIs treatment.^[45, 46] For patients with reflux after POEM, Guidelines give its advice on the use of PPIs. The European guidelines suggest that POEM should be administered with a double dose of PPIs for 2-4 weeks postoperatively to promote mucosal healing.^[47] Thereafter, the

European guidelines recommend long-term treatment with PPIs for patients with symptoms of reflux and reflux esophagitis.^[47] However, a few patients do not respond well to PPIs therapy, called refractory GER. The pathogenesis of is unclear, but a recent study suggests that genotype cytochrome P450 2C19 (CYP2C19) variability may affect the efficacy of PPIs. A single-center cohort study has found that about 55% of patients with refractory GER have been identified with rapid metabolizers of CYP2C19 variability. Therefore, for those patients, PPIs, which is less affected by CYP2C19 pharmacogenetics, are needed.^[48]

Improvement of POEM Procedure for Prevention of GER

Some endoscopic specialists have suggested different solutions in POEM procedure to avoid GER. Since POEM may damage the oblique muscle and increase the incidence of GER after POEM, protecting the oblique muscle is an effective measure to control GER after POEM. Studies have shown that two penetrating vessels are a new indicator of myotomy site.^[49] A study of retaining oblique muscle in POEM with two penetrating vessels as anatomical markers showed that this method can significantly reduce the occurrence of post-POEM GER (31.3% vs 58.1%, $P = 0.017$).^[50] In addition, a study in a Western cohort, including 23 patients using two penetrating vessels for guiding myotomy, has proved that a majority of patients (82%) has no GERD symptoms after POEM.^[51] Besides that, a statement of post-POEM GER international multi-center experience suggests that the recommended length of POEM is 2-3cm when the gastric cardia is incised.

Endoscopic Intervention Against Reflux

In addition to the above-mentioned methods of drug therapy and improvement of POEM procedure, there are also three new endoscopic methods for treating GER after POEM. POEM and fundoplication (POEM+F) are a new endoscopic technique proposed by professor Inoue, which is a good approach by combining the conventional

POEM with endoscopic fundoplication.^[52] A study of 21 patients using POEM+F to prevent GER noticed that almost all patients could see the wrap across gastroesophageal junction visually during endoscopic fundoplication with no complications. This technique was also carried out in India.^[53] After 1-year follow-up including 23 patients, nineteen patients could see complete EGJ fundoplication under the endoscope, and four patients showed grade A reflux esophagitis without GER symptom.^[54] A novel treatment for refractory gastroesophageal reflux disease called C-BLART (clip band ligation anti-reflux therapy) has established by Linghu professor, which suggested that about 43% of the patients in C-BLART group stopped PPIs treatment in 6 months after surgery.^[55] C-BLART is a promising treatment for post-POEM GER, however there is no trial to prove that. Trans-oral incisionless fundoplication (TIF) is a new endoscopic technique applied to patients with GER after POEM. A study included 5 patients with post-POEM GER, and followed up for almost 2 years. Results showed that all patients have esophagitis relieved, which proves that TIF has a good short-term effect on POEM GER after TIF.^[56] However, this procedure has a lack of sample size and short follow-up time, we don't recommend all patients of GER to think about endoscopic intervention. In addition, focusing on treatments for esophageal motility for patients in achalasia, an experiment in animal has founded that implantation of esophageal electrodes and pacemaker can induce esophageal intraluminal pressure changes, which may improve esophageal peristalsis.^[57] This field still needs more studies to prove it in the future.

CONCLUSION

Gastroesophageal reflux is a common long-term complication after POEM. GER after POEM is significantly higher than laparoscopic Heller's myotomy and pneumatic dilatation. The reasons of high risk of post-POEM mainly include own characteristics of POEM procedure and esophageal motility characteristics of achalasia. There are so many predictors of GER after POEM, mainly about baseline data, factors related to POEM procedure and some post-POEM motility index. In addition, the diagnosis of post-POEM GER are comprehensive judgments of reflux symptom, endoscopy and

24-hour pH testing. We should make it clear that the abnormality of 24-hour pH testing is due to real reflux or food fermentation. If patients have real reflux, we need to use PPIs for treating GER after POEM. However, if patients have food fermentation, we need to do some examinations to assess the effect of POEM and determine whether additional surgery is needed. Most post-POEM GER can be relieved and improved by using PPI drugs, and the incidence of post-POEM GER can also be declined by adjusting operative factors. Some refractory GER patients may be rapid metabolizers of CYP2C19 variability. Therefore, for those patients, they need PPIs, which is less affected by CYP2C19 pharmacogenetics, or additional TIF surgery and fundoplication. Endoscopic intervention against post-POEM reflux just has small sample size of studies and needs to be confirmed in long-term, large-sample clinical trials.

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