Peroral endoscopic cardial constriction in gastroesophageal reflux disease

Hai-Qing Hu, PhD, Hui-Kai Li, PhD, Ying Xiong, PhD, Xiao-Bin Zhang, MD, Jun-Li Zhi, BS, Xiao-Xiao Wang, BS, En-Qiang Ling-Hu, PhD

1. Introduction

Gastroesophageal reflux disease (GERD) is a common chronic disease that has a variety of clinical manifestations. Typical symptoms include acid reflux and heartburn, which impair life quality. Efficient therapy for GERD may decrease the incidence of GERD-related complications and improve life quality. Therapeutic approaches to GERD include lifestyle modification, medical therapy, endoscopic therapies, and surgical treatments.[1] Due to economic burden, complications of pharmacological treatments and complications of surgical treatments, GERD therapy remain as a challenge.[2,3] Proton pump inhibitors (PPIs) and laparoscopic fundoplication were used constantly for GERD by the main mechanism to inhibit the secretion of gastric acid and anti-reflux effect in esophagostrophic junctions. However, PPIs had a poor curative effect and easy recurrence after treatment for some patients.[4] The laparoscopic gastric folding technique can solve the problems of the recurrent symptoms because of its high surgical trauma and the problem of adverse reactions and poor patient compliance. During the development of endoscopic treatment technology, endoscopic radiofrequency and endoscopic gastropasty replaced traditional treatment minimally invasive technology.[5] Peroral endoscopic cardial constriction (PECC) is new endoscopic technology that is less invasive for GERD. The basic principle of PECC is the ligation of the mucosa, the necrosis of inherent muscular at the submucosal part to form the scarring of surgical treatments, GERD therapy remain as a challenge.[12–14] PECC is a feasible, safe, and effective method to treat GERD through narrowing the diameter of the cardia and preventing the reflux of stomach contents.

Keywords: gastroesophageal reflux disease, endoscopic treatment, peroral endoscopic cardial constriction.

2. Patients and methods

2.1. Study design

This study began in March 2014, after which a preliminary follow-up study was conducted until April 2015 on patients treated with PECC in the initial single center. Approval for these studies was granted by the medical ethics committee of Chinese PLA General Hospital (S2013–02) and Chinese Clinical Trial Registration (ChiCTR-TRC-14004796). Written informed consent was obtained from all patients. An approval was obtained before the start of the original study and another one
was obtained during the short-term follow-up period. All patients have been treated with PPI treatment, and symptoms of the patient are repeated. We compared 24-hour esophageal pH monitoring, esophageal kinetics testing, endoscopy, gastroesophageal reflux disease-questionnaires, and gastroesophageal reflux disease-health related quality of life before and after surgery. The results were compared with the currently accepted PPI efficacy (standard control). We were enrolled in 16 patients, one of which gave up follow-up to conduct laparoscopic fundoplication in the local hospital. The other 2 patients were missing a review result. So, three cases were removed. The primary study objective was to determine the safety and efficacy of PECC for the treatment of symptomatic GERD. Primary 3- and 6-month efficacy was determined through analysis of the validated GERD-HRQL [10,11] and esophageal pH monitoring. The study design summary is summarized in Tables 1 and 2.

### 2.2. Study eligibility

Patients with a history of heartburn or regurgitation requiring daily PPI therapy were eligible. In addition, all patients met the following inclusion criteria: patients with chronic GERD (>6 months) with typical symptoms (acid regurgitation, heartburn); patients who were aged 18 to 75 years; patients with pathological 24-hour esophageal pH monitoring; patients with a DeMeester score >50; patients with normal or hypotonic LES pressure (>5 mm Hg); and patients with recurring typical symptoms and/or not been relieved after 2 months of systematic medical therapy.

Exclusion criteria for the procedure were as follows: patients with Barrett epithelium or early-stage esophagus cancer diagnosed by pathological biopsy; patients with previous endoscopic or surgical anti-reflux procedure and pregnancy; patients with a hiatal hernia diameter of >3 cm; patients with severe cardiopulmonary infection; patients with nonerosive reflux disease (NERD); PPI was used more than 3 times, and continuous use of PPI for more than 3 days would be removed; and exclude other esophageal motility disorders.

### 2.3. Baseline assessment and follow-up

During the baseline evaluations, patients completed the gastroscopy, GERD-HRQL, ambulatory pH studies, and esophageal manometer at pre-procedure (Table 3). Baseline upper endoscopy was performed to determine hiatal hernia size and esophagitis grade. The GERD-HRQL score assessed heartburn severity and the impact of GERD-specific symptoms on the quality of life of the patient using the scale. Primary efficacy and treatment response were assessed using the GERD-HRQL score. Patients were considered responsive to PECC treatment at 3 and 6 months when their GERD-HRQL score improved by 50% or more beyond the pretreatment baseline. Ambulatory endoscopy and esophageal manometry were also conducted for patients who had undergone these tests within the previous 6 months. Patients were reevaluated by completing the GERD-HRQL score, endoscopy, esophageal pH, and manometry studies at 3 and 6 months post-procedure. The patients were satisfactory with the improvement of GERD symptoms by telephonic follow-up. Satisfaction: symptom relief rate ≥60%; basic satisfaction: remission rate of 59% to 21%; dissatisfied: remission rate ≤20%. The difference

### Table 1

**Study design.**

| Pre-procedure | PECC | 3-mo | 6-mo |
|---------------|------|------|------|
| DeMeester     | ✓✓   | ✓    |      |
| GERD-HRQL     | ✓✓   | ✓✓   |      |
| Esophageal pH/manometry | ✓✓ | ✓✓ |      |
| EGD           | ✓✓   | ✓✓   |      |

Overview of study design.

EGD = esophagogastroduodenoscopy, GERD-HRQL = gastroesophageal reflux disease-health related quality of life, PECC = peroral endoscopic cardial constriction.

### Table 2

**The GERD-HRQL instrument.**

- Scale: No symptoms 0; Symptoms noticeable, but not bothersome 1; Symptoms noticeable and bothersome, but not every day 2; Symptoms bothersome every day 3; Symptoms affect daily activities 4; Symptoms are incapacitating, unable to do daily activities 5
- **Questions**
  1. How bad is your heartburn? 0 1 2 3 4 5
  2. Heartburn when lying down? 0 1 2 3 4 5
  3. Heartburn when standing up? 0 1 2 3 4 5
  4. Heartburn after meals? 0 1 2 3 4 5
  5. Does heartburn change your diet? 0 1 2 3 4 5
  6. Does heartburn wake you from sleep? 0 1 2 3 4 5
  7. Do you have difficulty swallowing? 0 1 2 3 4 5
  8. Do you have pain with swallowing? 0 1 2 3 4 5
  9. Do you have bloating or gassy feelings? 0 1 2 3 4 5
  10. If you take medication, does this affect your daily life? 0 1 2 3 4 5

| How satisfied are you with your present condition? | Satisfied | Neutral | Dissatisfied |
|--------------------------------------------------|-----------|--------|-------------|

It is a 10-question instrument that examines the intensity and frequency of heartburn, difficulty swallowing, bloating, and the burden of GERD medication. Answers are graded from 1 to 5, with a maximum total score of 50.

### Table 3

**Baseline patient characteristics.**

| Patient no (n) | Gender (Female/male) | Age, y (range) | GERD symptom duration: n (%) | Daily PPI use, n (%) | GERD symptom duration: y | LA classification A/B/C/D | Hiatal hernia (%) | Overall satisfaction |
|---------------|----------------------|---------------|----------------------------|---------------------|--------------------------|------------------------|------------------|-------------------|
| 13            | 9/4                  | 53 (40–70)    | 7 (54)                     | 6 (46)              | 13 (100)                 | 6/6/1/0                | 1 (7)            | –                 |

Baseline data for GERD with clinically indicated endoscopy. GERD = gastroesophageal reflux disease.
between satisfied and dissatisfied patients was statistically significant 3 months and 6 months before and after surgery.

2.4. Peroral endoscopic cardial constriction (PECC) protocol

All procedures were performed in our institution. All procedures were performed by the same endoscopist. The procedure was carried out using a forward-viewing endoscope of outer diameter 9.8 mm (GIFH260; Olympus, Tokyo, Japan) and an endoscopic ligation device (MBL-6-F; COOK Ireland Limited; National Technogy Park Limerick, Ireland) and resolution clips (Resolution Clip; Boston Scientific corporation, Massachusetts, Natikeshi).

(1) Preparation before procedures: without diet and water for 6 hours.
(2) General anesthesia: All procedures were performed under intravenous propofol and ketamine sedation with the continuous monitoring of vital signs [blood pressure, electrocardiograph (ECG), and SO2; propofol: 6–12 mg/kg per hour; ketamine: 1–2 mg/kg was instituted].
(3) PECC: esophagogastroduodenoscopy (EGD) was performed using a video-endoscope, and esophageal varices ligation equipment was fixed upon endoscopy. Two single-band ligation devices (Fujinon, Japan) were placed at the greater curvature and lesser curvature of the far-end of the esophagus under endoscopy guidance, respectively. The first plication was positioned approximately 1.0 cm above the cardia along the lesser curvature. A second plication was placed 1.0 cm above greater curvature.
(4) Fixation: fixed the 2 ends of the ligation devices with Resolution clips (Boston Scientific).
(5) Medical therapy after treatment: oral administration of 20 mg of omeprazole twice a day for 2 weeks. The process was performed by 2 experienced digestion physicians.

2.5. Statistical analysis

Primary efficacy was based on the results of the GERD-HRQL questionnaire score. Quantitative data were expressed as mean ± standard deviation (SD). Patients were considered treatment responders if they achieved at least 50% improvement in their 3- and 6-month GERD-HRQL score, compared with their off-medication baseline. The GERD-HRQL and DeMeester score were analyzed using Student 2-tailed t test. P < .05 was considered statistically significant. The PECC treatment was considered a success for a given study outcome when the statistical test rejected the null hypothesis at a 1-sided P value of .05 or less. These statistical analyses were performed using SPSS 17.0 software package (SPSS Inc., Chicago, IL).

3. Results

3.1. Patients and baseline characteristics

Patient baseline characteristics are summarized in Table 3. A total of 13 patients successfully underwent the PECC procedure and completed the 3- and 6-month follow-up. To date, none of these patients reported any severe complication related with the PECC treatment. However, 5 patients experienced slight chest pain symptoms that disappeared 1 day after treatment without medical therapy. The GERD-HRQL scale and esophageal pH monitoring were applied to assess its clinical efficiency at 3 and 6 months after PECC treatment, respectively. The 13 GERD patients who were diagnosed according to the International Consensus of GERD diagnosis and Management for GERD (9 males and 4 females; range: 40–70 years, with a mean 53.31 ± 10.45 years) were enrolled into this preliminary study conducted from March 2014 to April 2015. There were 7 patients with more than 5 years of chronic GERD history and 6 patients with 6 months to 5 years of chronic GERD history. All PECC treatments were performed at our institution with approval from the institutional ethics committee. Written informed consent was obtained from all patients upon enrollment (Figs. 1–3).

3.2. Efficiency evaluation and follow-up

The GERD-HRQL questionnaire score, gastroscopy, 24-hour esophageal pH monitoring, and dynamic inspection were used to evaluate short-time clinical efficiency at 3 and 6 months, as well as every 6-month interval, subsequently after PECC treatment, respectively.

3.3. Comparisons of the GERD-HRQL questionnaire score before and 3 and 6 months after PECC treatment in GERD patients

The GERD-HRQL questionnaire score was used to evaluate the frequency and serious degree of heartburn and acid regurgitation for diagnosing GERD in clinic. Although the GERD-HRQL questionnaire score is a subjective index, it reflects the life quality of GERD patients. In this study, GERD-HRQL questionnaire

Figure 1. Move up of dentate line and the relaxation of cardiac ostium were shown under endoscopy in (A), and esophageal hiatus is shown in (B).
scores decreased significantly after PECC treatment, compared with before. As summarized in Table 4, the mean GERD-HRQL questionnaire score was 18.92 ± 7.89 before PECC treatment, and 4.46 ± 4.31 and 5.69 ± 5.07 at 3 and 6 months after PECC treatment, respectively. There was a significant difference between before and after 3 months and before and after 6 months after PECC treatment (P < .05). Furthermore, there was no significant change in GERD-HRQL scores between 3 and 6 months after PECC treatment (P > .05). This result suggests that PECC treatment could change the life quality of GERD patients, and its clinical efficiency was stable.

3.4. Comparisons of results of 24-hour esophageal pH monitoring before and at 3 and 6 months after PECC treatment in GERD patients

The DeMeester score (composite score of pH < 4 for upright, recumbent and total, number of reflux episodes in 24 hours, number of reflux episodes > 5 minutes, and the longest episode) is used by many gastroenterologists and gastrointestinal surgeons in the final interpretation of pH-metry. The DeMeester score is an objective index to reflect the severity of GERD, and is often used to evaluate the clinical efficiency of therapies. In this study,
the DeMeester score was detected to have a significant decreasing trend after PECC treatment in GERD patients compared with before treatment. The DeMeester score was 125.50 ± 89.64 before PECC treatment, and 16.97 ± 12.76 and 20.32 ± 15.22 at 3 and 6 months after PECC treatment, respectively. Furthermore, the difference between before treatment and at 3 months after PECC treatment, as well as between treatment and at 6 months after PECC treatment was statistically significant (P < .05). However, there was no significant changes between 3 and 6 months after PECC treatment in DeMeester scores (P > .05). In the pre-procedure esophageal pH monitoring of patients, the fraction times of a pH of <4 was 35.55 ± 26.20. This indicates the presence of severe acid reflux. Furthermore, these were 7.96 ± 13.03% and 4.72 ± 3.78% at 3 and 6 months post-procedure, respectively. Moreover, for the number of reflux episodes, the number of long reflux episodes, and the longest reflux episode, these results suggest that PECC treatment could change the status of gastric acid secretion and the acid environment of the esophagus in GERD patients, and clinical efficiency was stable.

### 3.5. Patient satisfaction at baseline

For patients on GERD medications, 77% of these patients were dissatisfied with the management of their GERD symptom. At 3 and 6 months post-treatment, 69% and 54% of patients reported satisfaction with the management of their GERD symptom, respectively (Table 5). Patients satisfaction had significant differences at the follow-up times compared with preproerational ones (P < .01) (Table 6).

### 3.6. Safety

There was no serious complication or death in our study. After PECC, a slight retrosternal pain and dysphagia occurred in 3 patients (13%). Endoscopy at 1 year after PECC revealed that the mucosal breaks disappeared in patients.

### 4. Discussion

GERD is a major digestive health problem due to its high and increasing incidence and its serious complications. Furthermore, it is one of the most frequent causes of gastroenterological consultations in out-patients, which significantly compromises the quality of life of patients.\(^{[13]}\) The management for GERD includes lifestyle modifications and weight reduction, anti-reflux medications and reduction of gastric acidity, endoscopic radio-frequency ablation and fundoplication, and laparoscopic fundoplication.\(^{[14]}\)\(^{[17]}\) Although these treatments have improved the prognosis of GERD, the management of GERD patients remains a very challenging task. For long-term complications and the economic burden brought about by anti-reflux medications and transient LES reducers led to the reduction of quality of life and brought inconveniences to the life of patients. The causes of GERD may include the following aspects. At first, reflux was synonymous with esophagitis and hiatus hernia. Second, it was a motility disorder defined by sphincter or peristaltic dysfunction. Third, it was an acid-peptic disorder. PECC is a new endoscopic method. The mechanism of PECC is through narrowing the diameter of the cardia, increasing the pressure of the esophageal sphincter, and preventing the reflux of stomach contents. In this preliminary study, there was no serious treatment-related complication reported. This suggests that PECC is a feasible and safe method for the treatment GERD. GERD-HRQL scores and results of 24-hour esophageal pH monitoring are commonly used in diagnoses and the evaluation of the efficiency of subjective and objective indexes in clinic.\(^{[18]}\)\(^{[23]}\) Hence, in this study, we analyzed the 2 indexes to assess the clinical efficiency of PECC for the treatment GERD. Results revealed that GERD-HRQL scores and results of the 24-hour esophageal pH monitoring signifi-

### Table 4

**Results of 24-h esophageal pH monitoring and GERD-HRQL.**

|                      | Pre-procedure | Post-procedure 3 mo | Post-procedure 6 mo |
|----------------------|---------------|---------------------|---------------------|
|                      | X ± SD        | X ± SD              | X ± SD              |
| DeMeester            | 125.50 ± 89.64 | 16.97 ± 12.76       | 20.32 ± 15.22       |
| Fraction at a pH < 4 | 35.55 ± 26.20 | 7.96 ± 13.03        | 4.72 ± 3.78         |
| No. of reflux episodes| 240.77 ± 158.77| 75.48 ± 54.47       | 111.84 ± 89.34      |
| No. of long reflux episodes | 16.23 ± 10.57 | 2.14 ± 2.28         | 1.13 ± 1.36         |
| Longest reflux episode, min | 84.92 ± 110.36 | 9.80 ± 7.94        | 4.65 ± 2.41         |
| GERD-HRQL            | 18.92 ± 7.89  | 4.46 ± 4.31         | 5.69 ± 5.07         |

Results of 24-h esophageal pH monitoring and GERD-HRQL compared before and after PECC.

**GERD-HRQL =** gastroesophageal reflux disease health-related quality of life.

### Table 5

**Patient satisfaction.**

| Patient satisfaction (%) | Pre-procedure | Post-procedure 3 month | Post-procedure 6 month |
|--------------------------|---------------|------------------------|------------------------|
| Satisfied                | 30            | 63                     | 71                     |
| Neutral                  | 55            | 16                     | 11                     |
| Dissatisfied             | 15            | 2                       | 8                      |

Compared patient satisfaction before and after PECC.

### Table 6

**Patient satisfaction (n%).**

| Cases (n) | Pre procedure | Post procedure 3 month | Post procedure 6 month |
|-----------|---------------|------------------------|------------------------|
| Satisfied | 13            | 9 (69)                 | 7 (54)                 |
| Neutral   | 13            | 3 (23)                 | 3 (23)                 |
| Dissatisfied | 13          | 10 (77)               | 1 (8)                  |
| P         | <0.01         | <0.01                  | <0.01                  |
cantly decreased after PECC, and clinical efficiency lasted for a long period of time. Furthermore, the frequency and degree of heartburn and acid regurgitation in GERD patients was reduced, and the quality of life of patients was significantly improved. In addition, DeMeester scores were reduced by PECC, which was reflected by the 24-hour esophageal pH monitoring and was an index for the acid environment in the esophagus. All these results suggest that PECC is an efficient method for the treatment of GERD. For 2 GERD patients, the evaluation of the GERD-HRQL score decreased, but the DeMeester score increased. The reason may be the examination sequence of 24-hour esophageal pH monitoring and gastroscopy. For 2 patients, the gastroscopy examination was performed before the 24-hour esophageal pH monitoring. On the first day, esophageal motility and 24-hour esophageal PH monitoring was conducted on the patient. On the second day, after completing the 24-hour esophageal PH monitoring, patients underwent endoscopy in order to avoid endoscopic stimulation of vomiting, which could cause a transient esophageal kinetics, to change the effect of the inspection.

Inoue et al.[22] described the technique of the anti-reflux mucosectomy (ARMS) procedure that targets circumferential mucosectomy at the cardia to induce constriction and reduce acid reflux. There are similarities with PECC. The incidence of postoperative stenosis was higher in ARMS, especially in circumferential ARMS. The surface of the wound in ARMS was larger, and operation time was longer, which even lasted for 176 minutes, while the operation time for PECC was shorter. Operating time on average was 76 minutes (42–124 minutes, n = 3) in the piecemeal ESMR group and 127 minutes on average (98–176 minutes, n = 7) in the ESD group. PECC is simple and easy to put into effect, and it can relieve reflux symptoms effectively.

The main factor influencing the efficacy was the depth of ligation, so we conducted animal experiments on the depth of ligation. Ligation technique is very mature, which has been widely used in endoscopic varicose veins ligation, esophageal intraepithelial neoplasia EMR. Because the depth of ligation is the main factor affecting the therapeutic effect, we have done animal experiments on the depth of ligation.

There are several limitations in this study. First, this is a preliminary clinical study and the number of GERD patients is relatively small. Only 13 patients were targeted for analysis of 16 patients who were enrolled in this study. Hence, further studies should enlarge the sample size and add comparison group to draw more convincing conclusions about PECC. Second, patients were followed up for a short observation period. A long-term follow-up is needed to prove the feasibility, safety, adverse reaction, and curative effect. Third, more evaluation measures and consistency standard procedure should be established to assess for clinical efficiency and decrease bias for endoscopist and estimator so as to be clinically popularized and applied.

In conclusion, PECC is a new endoscopic method, and its mechanism is through narrowing the diameter of the cardia, increasing the pressure of the esophageal sphincter, and preventing the reflux of stomach contents. In this preliminary study, results suggest that PECC is a feasible, safe, and efficient method for the treatment of GERD.

**Author contributions**

**Conceptualization:** H-Q. Hu.

**Data curation:** E-Q. Ling-Hu, H-Q. Hu, H-K. Li, J-L. Zhi, X-B. Zhang, X-X. Wang, Y. Xiong.

**Writing – original draft:** H-Q. Hu.

**Writing – review & editing:** E-Q. Ling-Hu, H-Q. Hu.

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