

# Peroral endoscopic pyloromyotomy is efficacious and safe for refractory gastroparesis: prospective trial with assessment of pyloric function ▶

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## ABSTRACT

**Background** Gastroparesis is a functional disorder with a variety of symptoms that is characterized by delayed gastric emptying in the absence of mechanical obstruction. A recent series of retrospective studies has demonstrated that peroral endoscopic pyloromyotomy (G-POEM) is a promising endoscopic procedure for treating patients with refractory gastroparesis. The aim of this prospective study was to evaluate the feasibility, safety, and efficacy of G-POEM.

**Methods** 20 patients with refractory gastroparesis (10 diabetic and 10 nondiabetic) were prospectively included in the trial. Patients were treated by G-POEM after evaluation of pyloric function using an endoscopic functional luminal imaging probe. Clinical responses were evaluated using the Gastroparesis Cardinal Symptom Index (GCSI), and quality of life was assessed using the Patient Assessment of Upper Gastrointestinal Disorders – Quality of Life scale and the Gastrointestinal Quality of Life Index scores. Gastric emptying was measured using 4-hour scintigraphy before G-POEM and at 3 months.

**Results** Feasibility of the procedure was 100%. Compared with baseline values, G-POEM significantly improved symptoms (GCSI: 1.3 vs. 3.5;  $P < 0.001$ ), quality of life, and gastric emptying ( $T_{1/2}$ : 100 vs. 345 minutes,  $P < 0.001$ ; %H2: 56.0% vs. 81.5%,  $P < 0.001$ ; %H4: 15.0% vs. 57.5%,  $P = 0.003$ ) at 3 months. The clinical success of G-POEM using the functional imaging probe inflated to 50 mL had specificity of 100% and sensitivity of 72.2% ( $P = 0.04$ ; 95% confidence interval 0.51–0.94; area under the curve 0.72) at a distensibility threshold of 9.2 mm<sup>2</sup>/mmHg.

**Conclusion** G-POEM was efficacious and safe for treating refractory gastroparesis, especially in patients with low pyloric distensibility.

ClinicalTrials.gov

NCT02779920

TRIAL REGISTRATION: Experimental study; prospective, single-center, pilot study NCT02779920 at [clinicaltrials.gov](http://clinicaltrials.gov)

**► Table 1** Results of previously published series on peroral endoscopic pyloromyotomy in refractory gastroparesis.

	Design	N	Technical success, %	Clinical success, % (n/N)	GES improvement, % (n/N)	Adverse events, n	Follow-up, months
Shlomovitz 2015 [17]	Retrospective	7	100	86 (6/7)	80 (4/5)	1 bleeding	6.5
Khashab 2017 [21]	Retrospective	30	100	86 (26/30)	78 (14/17)	1 capnoperitoneum 1 ulcer	5.5
Gonzalez 2017 [33]	Retrospective	29	100	75 (M3) 69 (M6)	87 (20/23)	5 pneumo-peritoneum 2 bleeding 1 Abscess 1 stricture	10
Dacha 2017 [22]	Retrospective	16	100	81 (M6)	100 (12/12)	0	6
Rodriguez 2017 [19]	Case series	47	100	Significant improvement	Significant improvement	0	3
GES, gastric emptying scintigraphy; M, month							

## Introduction

Gastroparesis is a chronic functional disorder characterized by delayed gastric emptying, in the absence of mechanical obstruction, and a variety of other symptoms [1]. It has a high prevalence in the United States (approximately 3%). Common etiologies of gastroparesis include diabetes and surgery. The major symptoms include nausea, vomiting, postprandial fullness, and early satiety, with impaired quality of life. In patients with diabetes, gastroparesis could be responsible either for uncontrolled diabetes mellitus and/or postprandial hypoglycemia as a consequence of a significant glucose imbalance.

Delayed gastric emptying has to be confirmed by scintigraphy and is defined as the percentage of the remaining radioisotope at 2 hours (%H2) >60% and at 4 h (%H4) >10% [2]. The treatment for gastroparesis includes a specific diet (frequent small meals with low fat and fiber content) and prokinetics drugs [3–5]. However, some of these drugs are associated with dangerous side effects (e.g. cardiac arrhythmia); tachyphylaxis can also occur, making them ineffective. There is currently no validated therapeutic alternative if these treatments fail.

The pathophysiology of gastroparesis is complex and involves antral, fundic or pyloric motor dysfunction. Indeed, pylorospasm has been reported in some patients [6], and a high fasting pyloric tone has been found in almost 50% of cases. Fasting compliance is low in patients with gastroparesis and negatively correlated with gastric emptying [7]. The procedures used to treat pyloric dysfunction, including botulinum toxin injection [8], surgical pyloroplasty [9], pyloric dilation [10], and transpyloric stenting [11, 12], have produced promising results in open studies but not in randomized studies [13, 14]. A new and simple procedure for selecting gastroparetic patients who are suitable for an endoscopic treatment that targets pyloric dysfunction is the endoscopic functional luminal imaging probe (Endoflip; Crospon, Galway, Ireland) [15, 16].

Among the possible endoscopic procedures, four recent small retrospective studies and one case series (► **Table 1**) have suggested the efficacy of peroral pyloromyotomy/gastric peroral endoscopic myotomy (G-POEM) for treating severe refractory gastroparesis [17–24]. However, the lack of a systematic evaluation of gastric emptying, the heterogeneity of the patients and follow-up procedures, the retrospective experimental design, and the lack of consistent procedures for assessing pyloric function can only be addressed by a well-designed prospective study. The development of a new therapeutic procedure could represent an important step forward for affected patients.

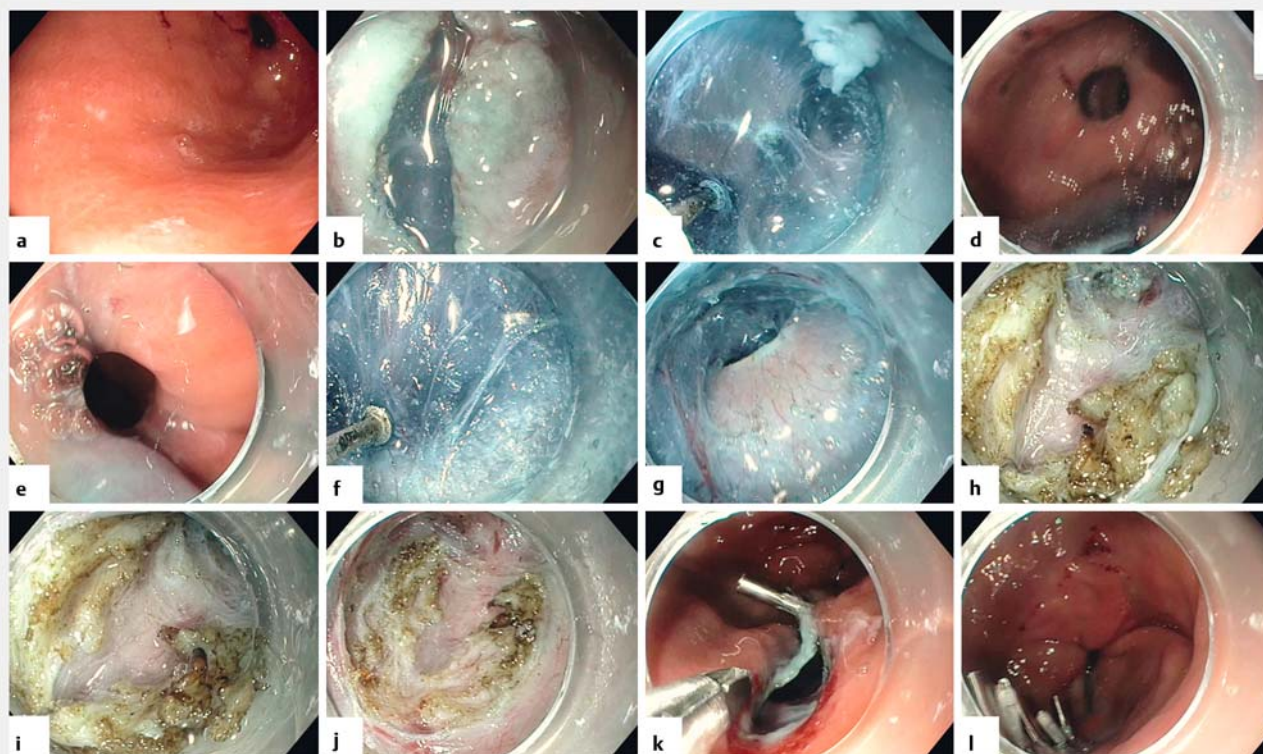
The aim of the current study was to evaluate the feasibility, safety, and efficacy of G-POEM in patients with refractory gastroparesis.

## Methods

### Study participants

We performed a prospective study to evaluate the technical success, safety, and efficacy of G-POEM for treating refractory gastroparesis at Limoges University Hospital from April 2016 to June 2017. This study was funded by the Protocole Hospitalier de Recherche Clinique Interrégional and approved by the institutional review board (NCT02779920). Gastroparesis was defined by confirming the association of symptoms with delayed gastric emptying at 4 hours (%H4 retention >10%) using gastric scintigraphy.

All patients included in this study were >18 years old and had moderate-to-severe refractory gastroparesis, defined as persistent symptoms and reduced quality of life despite 6 months of continuous treatment, including at least two of the three drugs that are available in France for treating gastroparesis (erythromycin, a motilin receptor agonist; domperidone or metoclopramide, dopamine receptor antagonists).



► **Fig. 1** Description of the procedure. **a** Identification of the pylorus. **b** Mucosal incision. **c** Submucosal tunneling. **d, e** Checking the direction of the tunnel. **f, g** Identification of the pyloric ring. **h, i** Pyloromyotomy. **j** End of the myotomy (pink serosa). **k, l** Closing the tunnel entry.

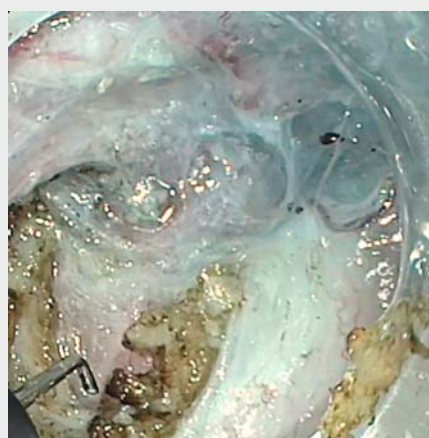
Gastroparesis was considered moderate to severe in cases of a Gastroparesis Cardinal Symptom Index (GCSI) score  $>2.6$ , refractory vomiting or a chronic diabetes imbalance with recurrent postprandial hypoglycemia. All patients provided written informed consent. Patients were excluded if they had a medical contraindication for gastroscopy or general anesthesia, or were taking anticoagulants or antiplatelet agents, or had a history of gastric surgery or a hemostatic disorder.

### Study design

All study participants were treated using G-POEM, according to a procedure published previously, with a submucosal tunnel performed along the greater curvature [21, 22] (► **Fig. 1**, ► **Video 1**). G-POEM was performed under general anesthesia with patients in the supine position and intubated. Immediately prior to the G-POEM procedure, pyloric function was evaluated using the Endoflip device by inflating the sleeve with 40 mL and 50 mL of liquid. Intubation was performed without curarization when possible. If curarization was necessary, celcurine was used because of its short half-life, and we included a delay of 20 minutes to confirm normal muscular neurotransmission using a TOF-Watch SX accelerometer (Organon Ltd., Dublin, Ireland) before taking the Endoflip measurements.

The Endoflip probe was passed along a high definition gastroscope, with a suture attached at the distal part of the probe, and grasped with biopsy forceps to help the probe through the pyloric channel under endoscopic visualization. Diameter,

cross-sectional area, pressure, distensibility, and compliance were measured or calculated by software at each balloon distension point for a minimum of 5 seconds.



► **Video 1** Peroral endoscopic pyloromyotomy.

Online content viewable at:

<https://doi.org/10.1055/a-0628-6639>

## G-POEM procedure

A high definition gastroscope with a transparent hood and carbon dioxide insufflation were used for the procedure. A glycerol solution was injected 4–5 cm from the pylorus, and a longitudinal mucosal incision was made using a T-type HybridKnife (Erbe Elektromedizin GmbH, Tübingen, Germany) and a VIO 200D using Endocut I current (Erbe Elektromedizin GmbH). A submucosal tunnel dissection was performed using a swift coagulation current. The scope was regularly withdrawn from the tunnel to check the tunneling direction. The submucosal vessels were coagulated using the HybridKnife or Coagrasper coagulation forceps (Olympus, Tokyo, Japan). After separation of the pyloric muscle arch, a myotomy was performed using a HookKnife (Olympus), dissecting from the duodenal to the gastric side with a safe traction technique. The myotomy was extended 1–2 cm along the antral muscularis propria until thin “pink” serosa was visible. The tunnel entry was then closed with hemoclips using the “zip” technique. The first hemoclip was placed on the distal part of the longitudinal incision. This first clip brought the edges of the incision closer. Then, the longitudinal incision was progressively closed using hemoclips, which caught the edges of the mucosal incision from the distal to the proximal part. If a perforation occurred, a nasogastric tube was positioned following the procedure.

Patients fasted on the day of the procedure; a liquid diet was provided the following day and a normal diet was resumed 2 days after the procedure. Patients were discharged 2–3 days after G-POEM. The evaluation of symptoms using GCSI, and quality of life using the Patient Assessment of Upper Gastrointestinal Disorders – Quality of Life (PAGI-QoL) scale and the Gastrointestinal Quality of Life Index (GIQLI), were performed the day before the G-POEM procedure, and at 1 and 3 months after the procedure. Postoperative Endoflip measurements and gastric scintigraphy were performed 3 months after G-POEM to evaluate gastric emptying.

## Study end points

The primary end point of the study was technical success, defined as the total number of successful procedures relative to the number initiated. Procedural success was defined as identifying the pyloric ring after submucosal tunneling and completing the pyloromyotomy.

The secondary end points were as follows.

- The safety profile of the G-POEM procedure: all adverse events (i. e. cause, severity, seriousness according to ICH E2A criteria and outcome). Adverse events were considered severe if a life-threatening condition, hospitalization, significant or sustained disability or any medically serious event was involved.
- Clinical success: decrease of at least 0.75 on the GCSI.
- An evaluation of the efficacy of G-POEM in terms of:
  - gastric emptying (scintigraphy at 3 months)
  - clinical symptoms (GCSI before and at 1 and 3 months after G-POEM); symptoms were evaluated using the GCSI, which uses a 6-point Likert scale ranging from none (0) to very severe (5). Based on the GCSI development data, a

total GCSI score >2.6 was used to define moderate disease, and a total GCSI score >3 was used to define severe disease

- abdominal pain and abdominal discomfort were evaluated using the same 6-point Likert scale, ranging from none (0) to very severe (5)
- quality of life (PAGI-QoL and GIQLI before, and at 1 and 3 months after G-POEM)
- Endoflip results.
- An evaluation of pyloric distensibility before and 3 months after G-POEM.

## Statistical analysis

Because this was a pilot study, no sample size calculation was performed. The study database was created using Oracle-based CLINSIGHT software ([www.ennov.com](http://www.ennov.com)) and the CS-DESIGNER module. The statistical analysis was performed using SAS software (ver. 9.3; SAS Institute, Cary, North Carolina, USA), and a *P* value of <0.05 was considered significant.

The differences between pyloric compliance and distension, gastric emptying half-time, and gastric retention at 2 and 4 hours, and the GCSI, GIQLI, and PAGI-QoL scores were analyzed using the Wilcoxon signed-rank test. Receiver operating characteristics curves were constructed using MedCalc statistical software (<https://www.medcalc.org/>) to estimate the ability of distensibility and compliance of the pylorus measured by Endoflip to predict the success of the G-POEM procedure.

All adverse events were coded based on verbatim notes of the investigator using the MedDRA dictionary v20.0.

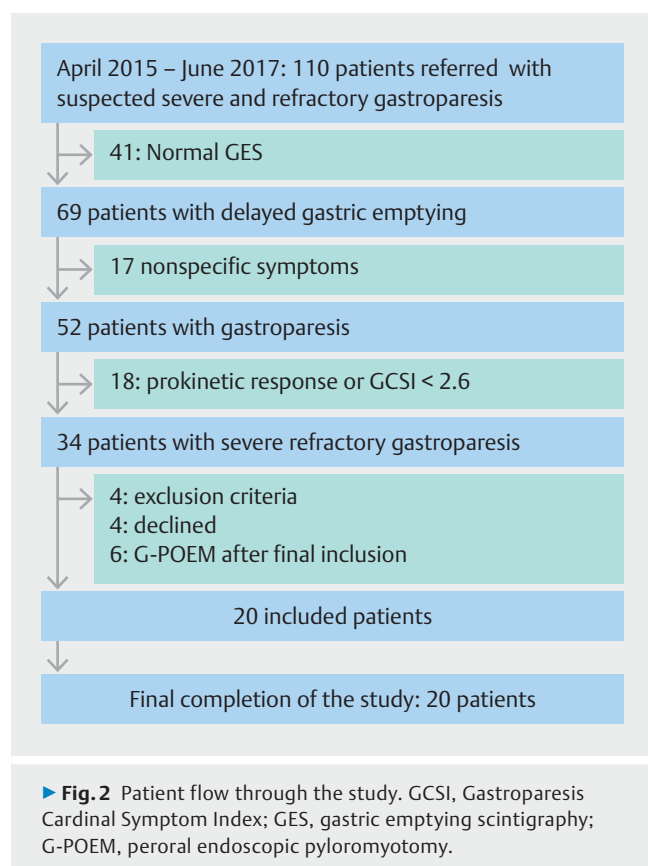
## Results

### Study population

A total of 110 patients were evaluated for suspected severe and refractory gastroparesis, and 20 were included between April 2016 and June 2017 (► **Fig. 2**). In total, 10 patients had diabetic gastroparesis, and 10 had nondiabetic gastroparesis. In this latter group, four patients (20%) had idiopathic gastroparesis, three (15%) had gastroparesis secondary to Sjögren's syndrome, one (5%) had postsurgical gastroparesis, one (5%) had gastroparesis secondary to Parkinson's disease, and one (5%) had gastroparesis secondary to systemic sclerosis. The median body mass index was 24.96 kg/m<sup>2</sup>. A total of 13 patients (65%) had a dedicated nutritional follow-up because of their gastroparesis. Despite this specialized monitoring, 35% (n=7) and 15% (n=3) of patients had lost at least 5% and 10% of their weight, respectively, in the preceding 6 months. One patient required enteral nutrition because of clinical malnutrition.

Overall, 16 patients (80%) had a GCSI>2.6, 15 (75%) had a GCSI>3, and 8 (40%) had a GCSI>4. Of the four patients with a GCSI<2.6, two diabetic patients had daily refractory vomiting, one diabetic patient had recurrent severe postprandial hypoglycemia due to severe gastric emptying, and one patient suffered from Parkinson's disease with failure of L-DOPA therapy, which was suspected to be linked to her confirmed severe delayed gastric emptying.





Median abdominal pain and median abdominal discomfort were 4.0 and 4.5, respectively.

Two patients (10%) had undergone previous botulinum toxin injection but had not responded to treatment, and no pa-

tients were subjected to gastric electric stimulation because in France there is no reimbursement for this two-therapy strategy. All patients had delayed gastric emptying with a %H4 median of 57%. At inclusion, the median total GCSI was 3.5 (interquartile range [IQR] 2.9–4.3), the median PAGI-QoL score was 3.0 (IQR 2.2–3.4), and the median GIQLI was 63.0 (IQR 55.0–76.0).

Data on pyloric function, measured using the Endoflip probe prior to the G-POEM procedure, were as follows (median; IQR):

- 40 mL distension volume: diameter 13.9 mm (12.4–15.4), pressure 12.7 mmHg (11.2–17.8), compliance 335.9 mm<sup>3</sup>/mmHg (271.0–419.0), area 152.5 mm<sup>2</sup> (120.0–184.5), distensibility 11.7 mm<sup>2</sup>/mmHg (8.3–15.8).
- 50 mL distension volume: diameter 17.3 mm (15.0–18.2), pressure 28.9 mmHg (24.0–32.1), compliance 235.6 mm<sup>3</sup>/mmHg (190.0–321.0), area 234.5 mm<sup>2</sup> (177.5–258.0), distensibility 8.1 mm<sup>2</sup>/mmHg (5.7–11.2).

### Primary end point

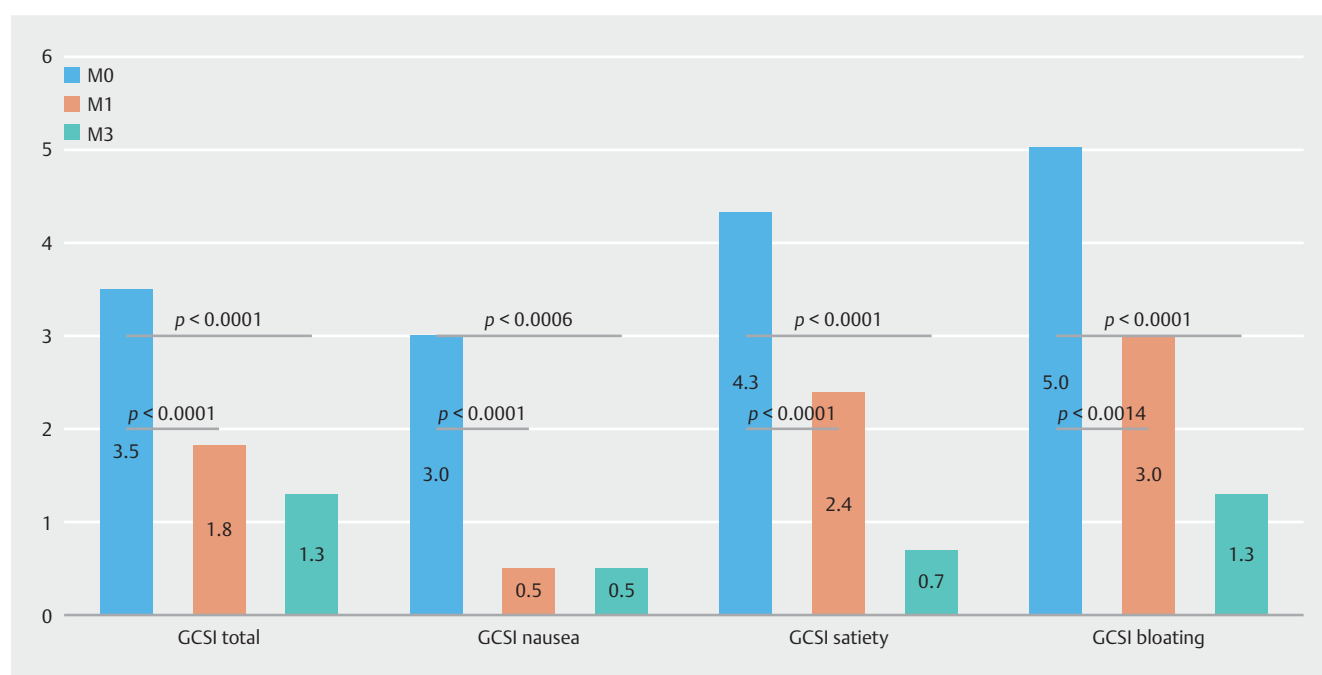
The technical success of the G-POEM procedure was 100%.

The median duration of the procedure was 56.5 minutes (IQR 48.5–67.0). The median durations of submucosal tunneling and myotomy were 23.0 minutes (IQR 20.0–28.5) and 17.5 minutes (IQR 15.5–21.0), respectively. The mean duration of inpatient hospitalization for the procedure was 3.75 days.

### Secondary end points

#### Clinical efficacy

We observed a significant improvement in the GCSI (► **Fig. 3**). The median preoperative GCSI was 3.5, and this improved to 1.8 at 1 month ( $P < 0.0001$ ) and 1.3 at 3 months ( $P < 0.0001$ ). All GCSI subscales (i.e. nausea, satiety, and bloating) improved



**Fig. 3** Clinical results. GCSI, Gastroparesis Cardinal Symptom Index; M, month.

significantly (► Fig. 3). About 90 % of patients showed a clinically significant improvement, defined as a decrease in the GCSI of at least 0.75. Individual responses are shown in ► Fig. 4. The median improvement in GCSI was 65 %, while seven patients (35 %) showed a >75 % improvement in their symptoms

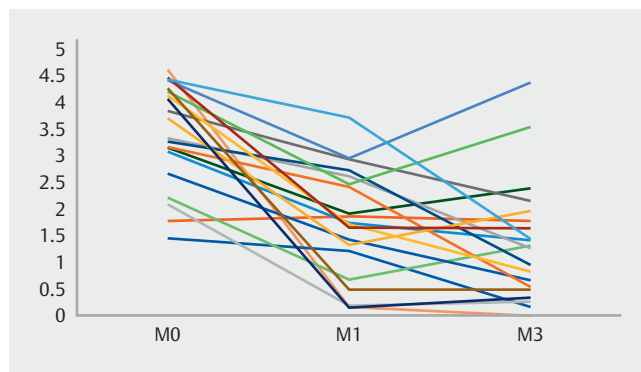
All individual symptoms, with the exception of retching, were significantly improved by G-POEM (► Fig. 5).

#### Quality of life evaluation

Patients treated using G-POEM reported significant improvements in their quality of life (► Fig. 6). The median preoperative PAGI-QoL and GIQLI scores of 3 and 63 improved to 4.1 and 97, respectively at 3 months ( $P<0.001$ ).

#### Efficacy in gastric emptying

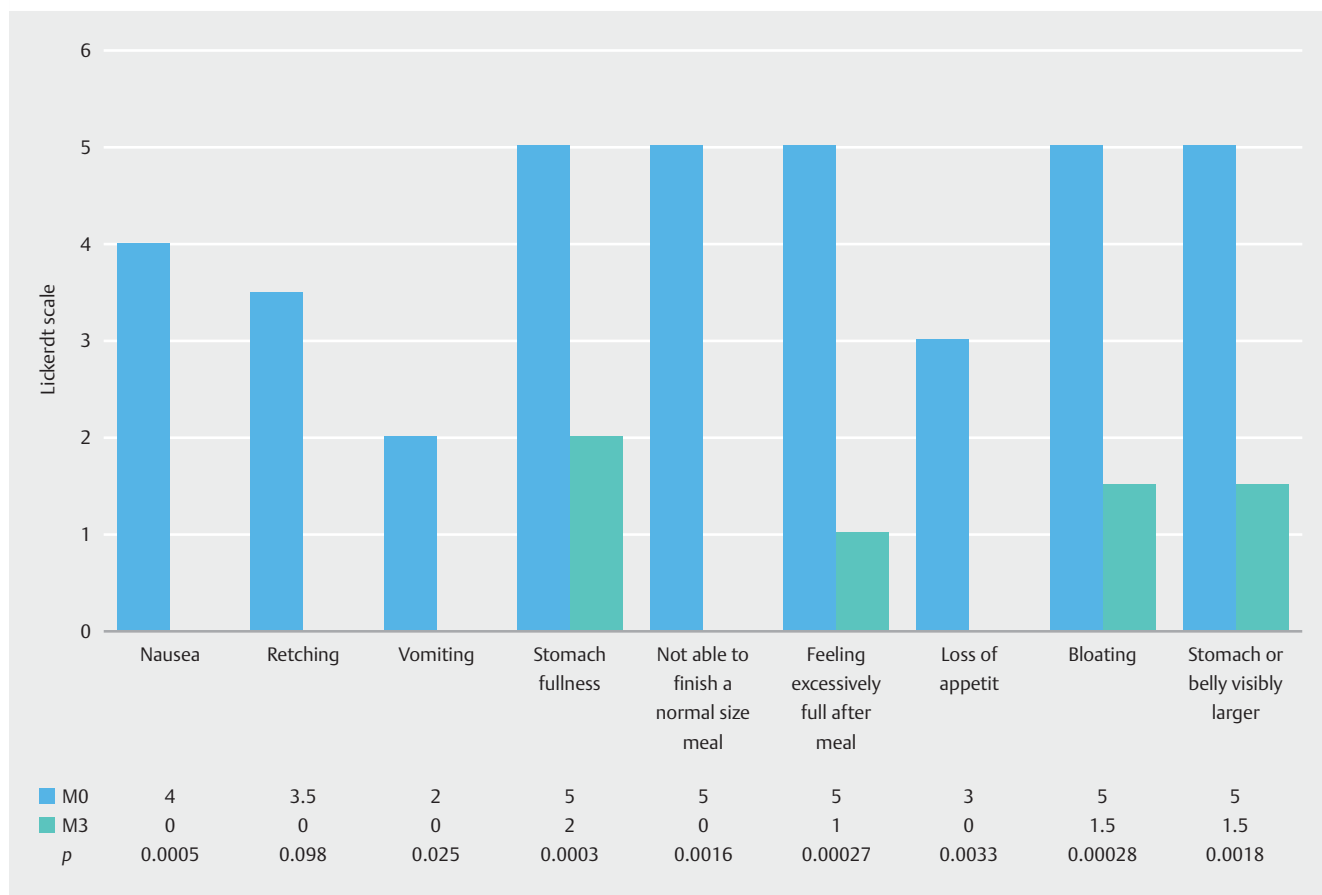
All scintigraphic parameters (half-life [ $T_{1/2}$ ], %H2, and %H4) improved significantly following G-POEM. The median  $T_{1/2}$  decreased from 345 minutes (IQR 130.5–374.5) to 100 minutes (IQR 73.5–256) at 3 months ( $P<0.001$ ). The %H2 decreased from 81.5 % (IQR 68–91.5) to 56.0 % (IQR 36.5–79.0;  $P=0.001$ ), and the %H4 decreased from 57.5 % (IQR 26.5–71.5) to 15.0 % (IQR 8.0–55.0) at 3 months ( $P=0.003$ ). The individual %H4 values before and after the G-POEM procedure are shown in ► Fig. 7. Six patients (30 %) had normal %H4 values.



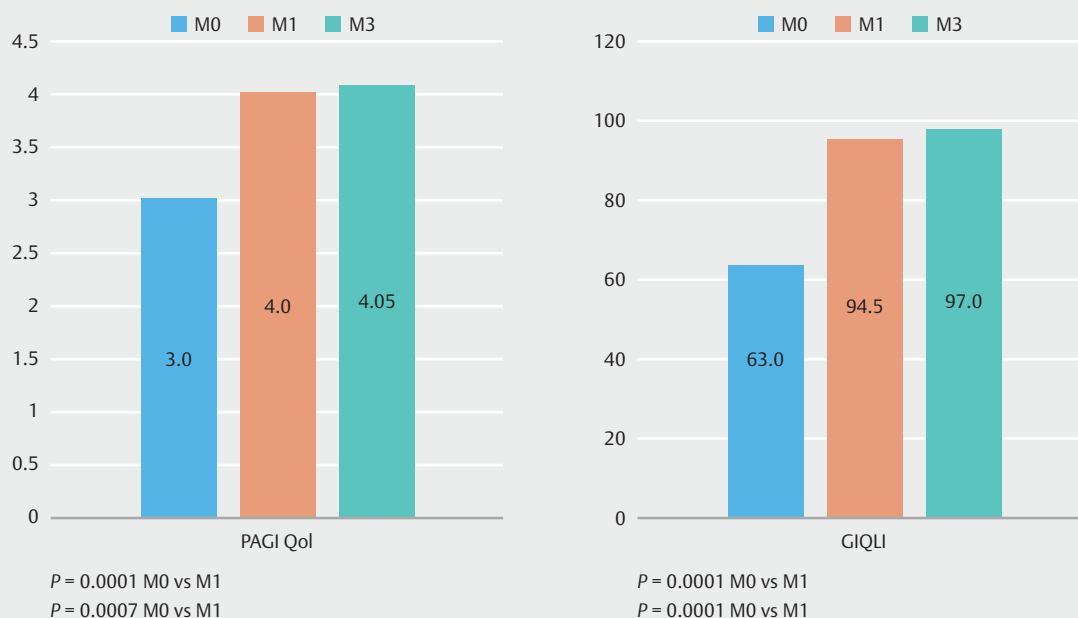
► Fig. 4 Individual changes in Gastroparesis Cardinal Symptom Index scores.

#### Evaluation of pyloric function before and after G-POEM

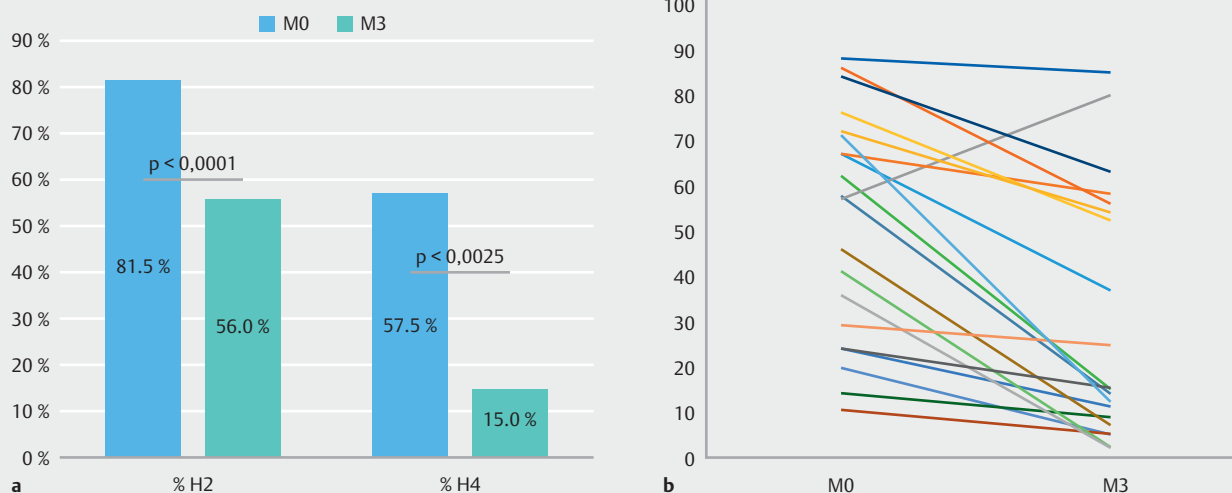
Prior to G-POEM, no correlation was found between the Endo-flip results and the GCSI scores or the results of gastric emptying, and no difference in pyloric function was observed between patients with and those without diabetes. At 3 months, the pyloric pressure measured with 50 mL of distension was significantly better in patients with diabetes than in those without (31.6 vs. 23.6 mmHg;  $P=0.03$ ).



► Fig. 5 Changes in individual symptoms of the Gastroparesis Cardinal Symptom Index. Median values are shown. M, month



► **Fig. 6** Quality of life evaluation. Median values are shown. M, month; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders – Quality of Life; GIQLI, Gastrointestinal Quality of Life Index.



► **Fig. 7** Gastric emptying scintigraphy (%H4) before and after peroral endoscopic pyloromyotomy. **a** Overall change. **b** Individual patients. M, month.

G-POEM was associated with a significant increase in both pyloric diameter (+1.6 mm in mean;  $P=0.01$ ), especially in patients with diabetes (+2.4 mm in mean;  $P=0.004$ ), and distensibility index (+2 mm<sup>2</sup>/mmHg in mean;  $P=0.04$ ), also especially in diabetic patients (+4 mm<sup>2</sup>/mmHg in mean;  $P=0.03$ ).

#### Evaluation of clinical efficacy according to pyloric function

Clinical efficacy was defined by improvements in the GCSI > 0.75. A pyloric 50-mL distensibility index < 9.2 mm<sup>2</sup>/mmHg was associated with a clinical efficacy of G-POEM with 100 % speci-

city and 72.2 % sensitivity ( $P=0.04$ ; 95 % confidence interval 0.51–0.94; area under the curve 0.72). The positive predictive value of this threshold was 100 %, but the negative predictive value was only 28.5 %.

#### Evaluation of the safety profile

A total of 28 adverse events, including six serious adverse events, occurred in 16 patients (► **Table 2**). A total of 20 adverse events were related to G-POEM, including one serious adverse event. This serious adverse event was severe abdominal

pain in a patient who had a perforation. Despite a normal blood test and a computed tomography scan, we decided to perform an explorative laparoscopy because the pain remained, even after treatment with strong opioid analgesics. The pain resolved a few hours after laparoscopy.

The other G-POEM-related adverse events included three cases of perforation; exsufflation of the capnoperitoneum was unnecessary, but a nasogastric tube was placed and antibiotics (amoxicillin and clavulanate) were administered for 5 days. Seven cases of per-procedure bleeding occurred but no transfusion was necessary; bleeding was managed using coagulation forceps and, in one case, using the plate of the T-type HybridKnife. No post-procedural bleeding occurred. There were eight cases of post-procedural abdominal pain at Day 1, which was managed easily by proton pump inhibitors and paracetamol. There was also one case of epistaxis. These adverse events affected 13 patients and all resolved without sequelae.

## Discussion

This is the first prospective trial evaluating G-POEM as a treatment for refractory gastroparesis with a concomitant assessment of pyloric function by the Endoflip device. It confirms the feasibility of the procedure when performed by endoscopists who are experts in endoscopic submucosal dissection.

Identifying the pyloric ring was straightforward in the current study, in contrast to a recent American study that used a radiopaque clip to locate the pylorus before beginning the procedure [18]. However, our team had previously practiced the procedure on pigs *in vivo*, and our assessments of the pathology of the pyloric muscle agreed with our endoscopic observations in every case [25].

The procedure was not lengthy (median duration 56.5 minutes), and the safety profile was very good, although three perforations occurred. In all cases, the perforations were “voluntary” because, in cases of doubt, we preferred to be sure that complete myotomy had been achieved in order to ensure effectiveness of the procedure. Per-procedure bleeding is generally not considered an adverse event in submucosal endoscopy, but the independent team monitoring adverse events preferred to mention them to ensure that the report was comprehensive.

As in previous retrospective studies, we observed both significant clinical and scintigraphic improvements in our patients. The median improvement in the GCSI was 65%, and 90% of patients reported a clinical improvement, defined as an improvement in the GCSI of at least 0.75. We chose  $>0.75$  reduction of GCSI as the cutoff for clinical success because it is the threshold that has been determined and validated in the international validation study of the GCSI. Several authors have defined clinical success as a reduction in GCSI of  $>1$  because they found this threshold to be more clinically relevant. When we used this threshold, the clinical success rate was 75%, which is still impressive for this disease. The use of this threshold is one of the strengths of our study because other studies on G-POEM only defined clinical improvement as a decrease in the GCSI without a cutoff for improvement.

The clinical and quality-of-life improvements observed in this study are based on scales validated by recognized international authorities (i.e. the GCSI, PAGI-QoL, and GIQLI). However, the study was not randomized or blinded. Many of the patients had been waiting for the procedure for several months and their refractory gastroparesis had been monitored over an extended period. Therefore, a placebo effect may have played a part in the clinical evaluations.

Nonetheless, the scintigraphic results are impressive. The median %H4 retention rate decreased from 57.5% to 15.0% at 3 months. At variance with the clinical evaluations, the scintigraphic findings are objective and the lack of randomization and blinding does not affect these results. Our results showed that G-POEM significantly improved gastric emptying. However, clinical improvement and acceleration of gastric emptying is often unrelated [26–28]. Our results are promising for many patients whose quality of life is affected by refractory gastroparesis.

Other endoscopic procedures (e.g. botulinum injection, transpyloric stenting, and pyloric dilation) and nonendoscopic procedures (e.g. gastric electric stimulation [29–32]) have shown promising results in open studies but not in blinded randomized trials. One possible reason for unsuccessful procedures might be the selection of patients entering the trials. Indeed, it can be difficult to identify those patients who will benefit most from a particular treatment, and it is not clear which patients benefited from treatment that targets pyloric function. Gastroparesis is a complex disease that is difficult to treat because of various etiologies and a lack of tools to evaluate gastric physiology. Endoflip is a promising method for the evaluation of pyloric function and the identification of gastroparetic patients with a pyloric dysfunction who could be the best candidates for endoscopic pyloric therapy. We identified a distensibility threshold of  $9.2 \text{ mm}^2/\text{mmHg}$  before the G-POEM procedure that predicted a clinical response with 100% specificity and 72.2% sensitivity. The positive predictive value of this threshold was 100%, meaning that all patients with a distensibility under  $9.2 \text{ mm}^2/\text{mmHg}$  reported a clinical success, defined as an improvement of GCSI of at least 0.75. Unfortunately, the negative predictive value was quite low (28.5%), meaning that in our study, Endoflip could only select patients that will respond to G-POEM but not patients who will fail to respond to the procedure. More well-designed studies using Endoflip are needed to confirm the potential of this tool in this indication.

Gourcerol et al. reported that a threshold of  $10 \text{ mm}^2/\text{mmHg}$  predicts the efficiency of pyloric dilation [7]. In that study, using the 90th percentile, the cutoff normality was  $10 \text{ mm}^2/\text{mmHg}$  in 27 healthy volunteers. They also found a lower pyloric distensibility in gastroparetic patients compared with healthy volunteers ( $16.2$  vs.  $25.2 \text{ mm}^2/\text{mmHg}$ ;  $P < 0.05$ ) with the Endoflip inflated to 40 mL. In our study, 45% of patients had a 40 mL distensibility that was lower than the threshold of  $10 \text{ mm}^2/\text{mmHg}$ . Moreover, the mean distensibility of 40 mL in our study was quite low at  $12.4 \text{ mm}^2/\text{mmHg}$ , lower than the  $16.9 \text{ mm}^2/\text{mmHg}$  in the study by Gourcerol.



► **Table 2** Safety analysis.

Adverse events <sup>1</sup>	Number of adverse events	Related to G-POEM	Severity
<b>Serious adverse events<sup>2</sup></b>			
Procedural pain	1	Related	Severe
Fecaloma	1	Not related	Moderate
Urinary retention	2	Not related	Mild
Sciatica	1	Not related	Severe
Subileus	1	Not related	Severe
<b>Nonserious adverse events</b>			
Procedural pain	8	Related	Mild (n = 6) Moderate (n = 2)
Procedural hemorrhage	7	Related	Mild
Gastric perforation	3	Related	Mild
Epistaxis	1	Related	Mild
Dyspepsia	1	Not related	Moderate
Ligament sprain	1	Not related	Mild
Wrist fracture	1	Not related	Mild

G-POEM, peroral endoscopic pyloromyotomy.  
<sup>1</sup> Preferred terms from the MedDRA dictionary (v20.0).  
<sup>2</sup> According to E2A criteria.

Endoflip can also be used just after the procedure to check the adequacy of the myotomy, as it has been for POEM in patients with achalasia.

However, this conclusion must be treated with caution. We did not have enough patients to confirm our threshold value, so larger studies investigating G-POEM with a systematic preoperative evaluation of pyloric function with Endoflip are required. Antroduodenal manometry may also be used to identify suitable patients; however, only one facility in France provides this service, and it is difficult to perform.

Patients who respond to pyloric toxin injections could be a good target for G-POEM because the therapeutic mode of action is theoretically similar. However, in our study, only two patients had prior botulinum toxin injections. Indeed, in France, pylorus botulinum toxin injections for refractory gastroparesis are not reimbursed, as there is a lack of controlled trial data. It has been proposed to be a compassionate treatment. Our hospital accepts financial support for this therapy only in exceptional cases after validation by a financial committee.

Because there were few patients in this study who failed to show clinical and scintigraphic improvement, we were unable to identify risk factors for the lack of a response to G-POEM. Gonzalez et al. [33] showed in univariate analyses that both diabetic and female patients have nonresponse risk factors at 6 months. Our results do not suggest that diabetes reduces the likelihood of treatment success; however, our nondiabetic patient group was heterogeneous and very different from the nondiabetic groups of previous series, which consisted mainly of patients with idiopathic and postsurgical gastroparesis.

Only one patient in our study had postsurgical gastroparesis after antireflux surgery, but this condition may be one of the most suitable etiologies for G-POEM because pyloric dysfunction may be linked to a surgical lesion on the vagus nerve, occurring during confection of the wrap; the vagus nerve injury increases pyloric tone.

The weaknesses of this trial are the lack of a sham procedure with which to compare clinical improvement, and the short follow-up, which was only 3 months. Long-term results are necessary because the effectiveness of the treatment may deteriorate over time. This is especially true in diabetic cases, because the etiological factors persist and gastroparesis is complex with a multifactorial pathophysiological process in these patients. All patients in this trial, and some new patients who have been treated since the end of this study, are now included in a longer-term follow-up investigation that includes clinical and scintigraphic re-evaluations over 5 years.

This prospective study confirmed the feasibility, safety, and potential efficacy of G-POEM for treating refractory gastroparesis, particularly in patients with low pyloric distensibility, as measured using Endoflip. Well-designed randomized trials and international prospective studies, with clinically relevant end points and evaluation of the underlying pathophysiology, are required. According to the difficulty and challenges linked to this complex disease, with multiple different pathophysiologies involved, our results must be interpreted with caution, particularly because 3 months is a short follow-up in the long history of a gastroparetic patient.

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## Competing interests

Jérémie Jacques is a consultant for Boston Scientific. Romain Legros is a consultant for Boston Scientific

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