

## G-POEM in Patients with Gastro paresis - Gambling for Healing or Bigger Armamentarium?

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### 1. Abstract

Despite the euphoria about the introduction of a novel and apparently successful treatment in gastroparesis, the amount of high quality data supporting the clinical utility of G-POEM are limited. Above all, the selection of patients with gastroparesis for G-POEM is problematic. Although these criteria fulfill the diagnostic criteria for gastroparesis, it is important to remember that symptoms of gastroparesis are non-specific and not necessarily (directly) caused by delayed gastric emptying. Moreover, G-POEM does not always accelerate gastric emptying and the mechanism by which this procedure improves symptoms has not been confirmed. Now that G-POEM has been added to the armamentarium of treatments for gastroparesis it is important that the indications for this procedure are established. Clear predictive factors for the success of this procedure have not been defined. Given the high prevalence of patients with dyspeptic symptoms, the invasiveness and the cost of the procedure (G-POEM is performed only by highly skilled endoscopists), this must be considered urgently. Currently, the diagnosis of gastroparesis is most commonly made by endoscopy (evidence of food retention, exclusion of stenosis) and gastric emptying scintigraphy. However, these diagnostic procedures do not identify the underlying causes of symptoms and disease. Gastric function is complex and delayed gastric emptying can be caused by impaired gastric contractility and impaired neuro-hormonal regulation of gastric emptying as well as pyloric outlet obstruction.

### 2. Introduction

Gastroparesis is diagnosed based on the presence of typical symptoms and evidence of delayed gastric emptying after mechanical obstruction has been excluded by endoscopy. Epidemiological data from the United States estimates the incidence of gastroparesis in the general population at 2.4 (in males) and 9.8 (in females) per 100,000 individuals [1]. As for the etiological cause, idiopathic diabetic gastropareses are most common diagnoses.

Cardinal symptoms include vomiting after food intake,

early satiety, gagging, nausea and upper abdominal pain. The symptoms of Gastroparesis can be standardized by the Gastroparesis Cardinal Symptom Index, which includes 9 different clinical criteria and is assessed by severity (GCSI, 0 to a maximum of 45 points, 2). Overall, the disease is associated with significantly reduced quality of life, but also increased mortality (e.g., by malnutrition or aspiration pneumonia, 3). The diagnosis is confirmed by the presence of delayed gastric emptying as defined by a validated gastric emptying study with established normal values (usually scintigraphy or 12C breathe test, 3). Minor delays in gastric emptying are common in

functional dyspepsia and the diagnosis of gastroparesis should be reserved for individuals with clinically relevant impairments of gastric function (at least x2 the upper limit of normal)[2].

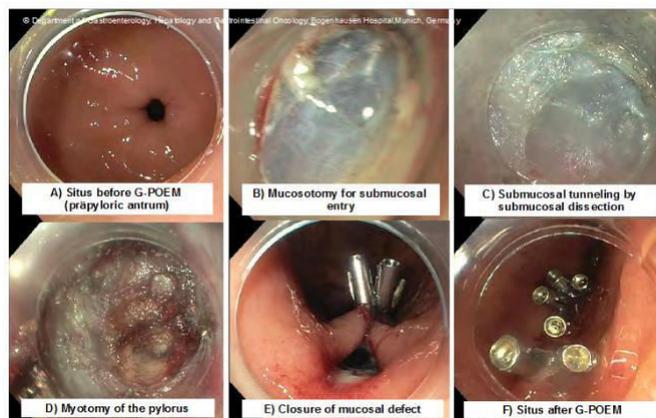
The pathophysiology of this disease is complex and multifactorial. Although the presence of delayed gastric emptying is required for the diagnosis it is not the cause of symptoms in most patients, indeed the association between this finding and patient symptoms is weak

(3). Moreover there is an important overlap between the diagnosis of gastroparesis and functional dyspepsia and the presence of psychological comorbidity can complicate the clinical assessment of this condition [3]. Notwithstanding these issues, studies have identified organic pathology in patients with this diagnosis. For example, in diabetic gastroparesis, in addition to the autonomic neuropathy of the vagus nerve, the reduction of pacemaker cells in the area of the large curvature and fibrosis of the gastric wall and pyloric sphincter have been documented. These histological and neuronal changes have been linked to various disturbances of gastric motility including dysfunction of the pylorus, hypomotility of the antrum and delayed accommodation of the fundus[3]. The expression of these pathological motility phenomena will differ depending on the underlying etiology, disease duration and co morbidities.

The underlying pathological basis of disease will also impact on the response to treatment and patient outcome. Empirical clinical management includes dietary measures (low-fiber, liquidized diet), tight blood glucose control in diabetes mellitus, and pharmacological therapy (e.g. prokinetics, antiemetics and analgetics; [3-5]). Although new drugs are being tested for the gastroparesis indication, the current drug options are very limited due to their low efficacy and spectrum of side effects. Approximately 30% of all affected patients do not respond to any available treatment modality [6]. For these individuals novel forms of treatment such as gastric high-frequency electrostimulation (Enterra) can be considered. This approach appears to reduce symptoms without improving gastric emptying; however, the cost-utility of this expensive and invasive treatment remains controversial [7].

### 1.1. Gastric Peroral Endoscopic Myotomy (G-POEM) as a New Principle of Therapy

The pathological significance of “outlet obstruction” at the pylorus region in selected patients with gastroparesis and the therapeutic potential of an intervention in this “therapeutic region of opportunity” (for example, by endoscopic dilatation or injection of botulinum toxin) has been confirmed by numerous case series[8]. First described gastric peroral endoscopic myotomy (“G-POEM”, antropyloomyotomy) with successful treatment outcome of one case as “proof of principle” of this method [8]. The technical implementation of G-POEM is comparable to POEM in achalasia in the esophagus (**Figure 1**). During the intervention, a catheter for the injection of the mucosa and a knife with a triangular tip (Triangle Tip Knife) are used alternately. After opening of the mucosa (usually about 5-7 cm proximal to the pylorus in the area of the large curvature), a stepwise submucosal tunneling (by dissection of the submucosa) is performed until the pylorus ring can be identified. The pyloric and longitudinal muscles of the pylorus are precisely split longitudinally (over a distance of two to three centimeters, “myotomy”) and finally the mucosal incision is closed with clips. The rationale of this procedure is a permanent repair of the pathologically disturbed pyloric region (by spasm or fibrosis), which causes the symptoms in a part of the patients with gastroparesis. Currently, two Meta-analyses have been published which summarize the technical feasibility and the results of the published studies on G-POEM [9-10].



**Figure 1:** Expiration of gastric oral endoscopic myotomy (G-POEM). The relevant technical steps of the procedure are represented by A - F (pictorial material: Department of Gastroenterology, Hepatology and Gastroenterological Oncology, Bogenhausen Hospital).

### 2. Methods

Real life data outside of published studies are currently only available to a limited extent. In this single-centre study, we retrospectively analyzed postprocedural clinical

improvement, technical success rate and procedural complications.

G-POEM was performed in 6 patients with therapy refractory gastroparesis (confirmed by gastric emptying scintigraphy) between 2018 and 2019. 5 patients were women. The age was 16-58 years (mean 36.3 years). The cause of gastroparesis was: diabetes in 2, idiopathic in 2 and postoperatively (after fundapplication) in 2 cases. In 4 patients, the implantation of a gastric electrostimulation without long-term therapeutic success was already carried out before so G-POEM was performed as lastline therapy. In all cases, the G-POEM has been successfully engineered by high-endoscopic technicians, with few complications except for minor post-interventional nausea and mild epigastric pain for a few days. In 3 patients there was a clinical improvement after G-POEM for a few weeks (<2). At a follow-up of 3-8 months, no patient reported relevant clinical improvement (subjectively and in GCSI). In 3 cases, gastric electrostimulation was restarted without any relevant clinical improvement.

### 3. Results

In this single center study, G-POEM showed a high technical success rate with a very low procedural complication rate. However, the clinical response beyond a short-term post-interventional improvement did not succeed in a single patient.

### 4. Discussion

The meta-analysis by [9] includes all publications on G-POEM with case numbers > 5 patients. In total, 7 studies (with a total of n = 196 patients) were evaluated in the period 2013 - 2019. According to the criteria of the National Institutes of Health (NIH), only 3 of them had a good study quality (small patient populations, only 2 prospective studies, only 3 randomized controlled trials). In terms of aetiology, idiopathic (42.3%) followed by diabetic gastroparesis (28.5%) were the most common cases treated. The follow-up in all studies was between one and 18 months. Primary outcomes were a) technical success rate and b) clinical response; secondary endpoints were c) improvement of GCSI and d) gastric emptying before and after intervention. The primary endpoint a) technical success rate was reached in 100%. The duration of the intervention averaged 69.7 minutes (95%

CI: 39-99 minutes). Overall, only 12 postinterventional and controllable adverse events (AEs) were reported (capnoperitoneum in 7, gastrointestinal bleeding in 2 cases), mortality was 0%. Clinical response was achieved in 82% (95% CI: 74-87%), but was defined by different parameters by different authors (e.g. avoiding further hospitalization, improving GCSI). A moderate but significant improvement in GCSI following G-POEM was observed in all studies, a significant improvement in gastric emptying was documented in 5/9 studies.

The review by [10] analyzed a total of 13 predominantly retrospective studies (with a total of 291 patients), some of which are also discussed in the meta-analysis above. Again, patients with treatment-refractory idiopathic (n = 93) and diabetic gastroparesis (n = 69) were most often included. The technical success rate was 100%, and clinical response occurred in 69 - 100% (GCSI improvement). The most common symptoms of nausea and vomiting were improved. This review also found a low and usually conservatively controllable rate of AEs (0-6.7%, excluding capnoperitoneum or pneumoperitoneum, gastrointestinal bleeding events). Only one study with n = 20 patients has so far described a relevant perforation rate of 20% (surgical intervention required in one patient)[11]. Overall, one death of G-POEM patient was reported across all studies, but this occurred independently of the intervention. Despite the euphoria about the introduction of a novel and apparently successful treatment in gastroparesis, the amount of high quality data supporting the clinical utility of G-POEM are limited. Above all, the selection of patients with gastroparesis for G-POEM is problematic. In the present studies, G-POEM was used as the ultima ratio in patients with refractory gastroparesis defined as GCSI > 1.5 for more than 6 months, no response to medication. Tests of gastric emptying were usually performed to confirm the diagnosis prior to the intervention. Although these criteria fulfill the diagnostic criteria for gastroparesis, it is important to remember that symptoms of gastroparesis are non-specific and not necessarily (directly) caused by delayed gastric emptying. Moreover, G-POEM does not always accelerate gastric emptying and the mechanism by which this procedure improves symptoms has not been confirmed. Now that G-POEM has been added to the armamentarium of treatments for gastroparesis it is important that the indications for this procedure are

established. Clear predictive factors for the success of this procedure have not been defined. Given the high prevalence of patients with dyspeptic symptoms, the invasiveness and the cost of the procedure (G-POEM is performed only by highly skilled endoscopists), this must be considered urgently. Currently, the diagnosis of gastroparesis is most commonly made by endoscopy (evidence of food retention, exclusion of stenosis) and gastric emptying scintigraphy. However, these diagnostic procedures do not identify the underlying causes of symptoms and disease. Gastric function is complex and delayed gastric emptying can be caused by impaired gastric contractility and impaired neuro-hormonal regulation of gastric emptying as well as pyloric outlet obstruction.

Advances in clinical imaging of gastric function, including new methodologies for the assessment of gastric emptying and the introduction of an endoscopic functional luminal impedance probe (Endoflip™) provide new opportunities to identify the causes of gastroparesis that could help guide targeted and effective treatment[12-14].

Endoflip measurements involve the endoscopic placement of a special balloon catheter connected to a high-resolution impedance-planimetry system to assess the luminal distensibility (luminal cross-sectional area in relation to pressure) of the pylorus examined. In addition, the closing function, length and diameter of the sphincter muscles can be measured [14]. Endoflip diagnostics may identify patients with “pylorus-dominant” gastroparesis related to functional (“pylorospasm”) or structural (stenosis) pathology that are, in principle, likely to respond to G-POEM or other treatments (e.g. dilatation) directly at relieving obstruction to flow at the pyloric sphincter.

A universal treatment concept, which provides “the one” satisfactory solution for all patients with gastroparesis, is still not available. The heterogeneity of the clinical picture, which represents a spectrum of different pathophysiological, etiological and clinical characteristics, still requires a therapy tailored to the individual patient. G-POEM should be considered especially in patients with pylorus-dominant gastroparesis. However, due to the invasiveness of the procedure, the application should initially be limited to experienced centers. For a sustainable assessment of this

procedure, the results of future prospective studies with a larger number of cases, longer follow-up and uniform optimized diagnostics, taking into account the respective gastroparesis phenotype, must be awaited.

## 5. Keypoints

- Approximately 30% of all affected patients suffering from gastroparesis do not respond to any available treatment modality. Gastric peroral endoscopic myotomy (G-POEM, antro-pyloromyotomy) represents a new principle of therapy.

- In this single center study, G-POEM showed a high technical success rate with a very low procedural complication rate. However, the clinical response beyond a short-term post-interventional improvement did not succeed in a single patient.

The heterogeneity of the clinical picture, which represents a spectrum of different pathophysiological, etiological and clinical characteristics, still requires a therapy tailored to the individual patient. G-POEM should be considered especially in patients with pylorus-dominant gastroparesis.

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