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IMPACT OF GASTRIC PER-ORAL ENDOSCOPIC MYOTOMY ON STATIC AND DYNAMIC PYLORIC FUNCTION IN GASTROPARESIS PATIENTS

SHORT TITLE: G-POEM IMPACT ON PYLORIC ENDOFLIP VALUES

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ABSTRACT

Background: Functional Lumen Imaging Probe (EndoFLIP) tests typically measure static pyloric parameters, but the pylorus exhibits phasic variations on manometry. Dynamic changes in pyloric function have not been quantified using EndoFLIP and the impact of Gastric Per-Oral Endoscopic Myotomy (G-POEM) on static and dynamic pyloric activity in gastroparesis is unknown.

Methods: EndoFLIP balloon inflation to 30, 40, and 50 mL was performed to measure mean, maximum, and minimum values and variability in pyloric diameter and distensibility before and after G-POEM in 20 patients with refractory gastroparesis. The impact of phasic contractions on these pyloric measures was compared.

Key Results: G-POEM increased mean ($P<0.0001$) and maximum ($P=0.0002$) pyloric diameters and mean ($P=0.02$) and maximum ($P=0.02$) pyloric distensibility on 50 mL EndoFLIP inflation but not intraballoon pressures or minimum diameters or distensibility. Temporal variability of pyloric diameter ($P=0.02$) and distensibility ($P=0.02$) also increased after G-POEM. Phasic coupled contractions propagating from the antrum through the pylorus were observed in 37.5% of recordings; other phasic activity including isolated pyloric contractions were seen in 23.3%. Variability of pyloric diameter and distensibility tended to be higher during recordings with phasic activity. Some pyloric responses to G-POEM were influenced by age, gastroparesis etiology, gastric emptying, and prior botulinum toxin injection.

Conclusions & Inferences: Pyloric activity exhibits dynamic changes on EndoFLIP testing in gastroparesis. G-POEM increases maximal but not minimal diameter and distensibility with increased variations, suggesting this therapy enhances pyloric opening but may not impair pyloric closure. Phasic pyloric contractions contribute to variations in pyloric activity.

Key Words: Contractility, gastric emptying, gastrointestinal motility, pyloromyotomy, pylorospasm.

KEY POINTS

- Variability of pyloric function has not been quantified using Functional Lumen Imaging Probes (EndoFLIP) and the impact of Gastric Per-Oral Endoscopic Myotomy (G-POEM) on static and dynamic pyloric activity in gastroparesis is unknown.
- Mean and maximum values and variations in pyloric diameter and distensibility are influenced by phasic contractions involving the pylorus; these measures are increased by G-POEM.
- The benefits of endoscopic myotomy in gastroparesis may result from enhanced pyloric opening without significant impairment of pyloric closure.

INTRODUCTION

Modulation of pyloric function may be effective treatment for gastroparesis. In an older manometry study, diabetics with gastroparesis exhibited increased phasic and tonic pyloric activity—a phenomenon termed pylorospasm (1). Pyloroplasties have been performed for years and pyloric botulinum toxin injections have been employed for two decades to improve gastric emptying in affected patients (2, 3, 4, 5, 6). Gastric per-oral endoscopic myotomy (G-POEM) has been described in recent case series and systemic reviews for gastroparesis therapy (7, 8, 9, 10).

Impedance planimetry measured by the Functional Lumen Imaging Probe (EndoFLIP) can quantify several pyloric motor parameters. EndoFLIP abnormalities in gastroparesis include reduced pyloric distensibility and diameter and increased pressure (11, 12, 13, 14). Abnormal pyloric diameter and distensibility have been correlated with increased vomiting, retching, early satiety, and fullness; reduced distensibility and increased pressure have been related to worse gastric emptying delays in gastroparesis (12, 13, 15, 16). G-POEM is reported to improve pyloric distensibility and pyloric dilation can enhance compliance (11, 16). EndoFLIP findings have been correlated with improved outcomes from pyloric therapies. One study saw greater improvements in early satiety after botulinum toxin injection in patients with increased baseline pyloric compliance and better pain reductions in those with higher baseline distensibility (12). Pyloric distensibility <9.2 mm^2/mmHg was found to have 100% sensitivity and 72.2% specificity for successful outcomes from G-POEM in gastroparesis (14).

All studies to date have reported single values for pyloric EndoFLIP parameters in gastroparesis reflecting either mean values or measurements at single time points. These findings do not consider pyloric motor variations seen on manometric studies (1). Others have

mentioned but not measured EndoFLIP pyloric variability in gastroparesis (16). Pyloric "motility waves" on EndoFLIP testing have been characterized in relation to meal and prokinetic drug stimulation in porcine studies (17). The relation of phasic pyloric activity to gastric emptying, gastroparesis etiology, demographic factors, and prior botulinum toxin injection and the differential effects of G-POEM on phasic vs. static pyloric motor parameters is unexplored.

This study characterized variabilities in pyloric function in gastroparesis using EndoFLIP and examined the impact of G-POEM on static and dynamic pyloric function. Specific aims included: (i) measure impact of G-POEM on mean, maximum, and minimum pyloric diameter, and distensibility, and mean pressure, (ii) quantify and relate variability of pyloric EndoFLIP measures to the presence of phasic pyloric contractions, and (iii) define clinical factors that predict improvements in pyloric diameter and distensibility with G-POEM. Some data in this report were presented at Digestive Disease Week in 2019 and at a meeting of the American Neurogastroenterology and Motility Society in 2019 (18, 19).

MATERIALS AND METHODS

Patient Population

Twenty adult gastroparesis patients with medication-refractory symptoms underwent G-POEM from June 2018 through July 2019 at University of Michigan Hospital. All patients reported symptoms of gastroparesis for at least 12 weeks. Gastroparesis was diagnosed based on abnormal scintigraphic testing. Seventeen patients underwent scintigraphy where delayed emptying was defined as >60% 2-hour retention and/or >10% 4-hour retention of a solid meal, while 3 patients underwent testing at outside institutions using different criteria to define gastric emptying delays (20, 21). Etiology of gastroparesis (diabetes, idiopathic, postsurgical) was determined by medical record review. Data relating to prior pyloric botulinum toxin injection were collected including if the therapy was given, how many injection sessions were performed, and the time (days) since the last injection session was conducted. G-POEM methods were stratified by whether they underwent single or double myotomy techniques.

All enrollment and analyses were approved by the hospital Institutional Review Board and all patients signed written informed consent forms prior to undergoing G-POEM and any data collection.

G-POEM Protocols

All G-POEM procedures were performed according to previously reported methods by the same therapeutic endoscopist (author RL) in a single endoscopy suite at University of Michigan Hospital (11, 22, 23). To minimize the risk of retained gastric food, all endoscopies were performed after a 3-day period of a liquid diet. Each patient underwent endotracheal intubation and was administered general anesthesia for the duration of the procedure using consistent protocols as deemed appropriate by the attending anesthesiologist. The patient was positioned in the left lateral position and a standard high-definition gastroscope prefitted with a clear cap (GIG-H190, Olympus America, Center Valley, PA) was orally introduced and diagnostic examination was performed. Carbon dioxide insufflation was used for the entirety of the endoscopic procedure. The gastroscope was withdrawn and then was reintroduced to carry the EndoFLIP catheter into the duodenum with positioning of the balloon across the pylorus. EndoFLIP measurement of pyloric function was conducted (see below), then the balloon was deflated and the EndoFLIP catheter was withdrawn from the patient. The gastroscope was reintroduced and passed to along the greater curvature of the stomach to a distance 5 cm proximal to the pylorus. An appropriate site was selected and 10 mL of a solution of methylene blue in normal saline was injected via a standard injection needle into the submucosal space. Using an endoscopic submucosal dissection knife, a 2 cm longitudinal mucosotomy was made with electrocautery (Endocut Q 3:1:1) into the submucosa. The gastroscope and cap were then used to separate the edges and access the submucosal space. A submucosal tunnel was then created to the level of the pylorus using alternating injection of methylene blue/saline and submucosal dissection with spray coagulation (Effect 2, 50 watts) or swift coagulation modes (Effect 3, 50 watts) to divide the submucosal fibers. The gastroscope was advanced to the pyloric ring where a pyloromyotomy was performed using Endocut Q. The myotomy was then extended proximally for an additional 2-3 cm to divide the circular muscle. For the first 13 patients, a single myotomy was performed. A dual myotomy technique was adopted for 6 of the 7 latter procedures based on emerging data from some centers which observed improved short-term clinical outcomes (24). After completion of the myotomy, the EndoFLIP catheter was again passed orally. The endoscope was reintroduced to carry the catheter into the duodenal sweep with repositioning of the balloon across the pylorus. EndoFLIP measurement of pyloric

function was conducted after G-POEM, then the balloon was deflated and the EndoFLIP catheter withdrawn from the patient. The mucosotomy site was closed with sequential endoclips and the procedure was completed.

EndoFLIP Methods

EndoFLIP recordings were obtained before and after G-POEM performance during the same endoscopic procedure. The EndoFLIP balloon (EF-325, Medtronic, Minneapolis, MN) was endoscopically positioned across the pylorus and was sequentially inflated to 30 mL, 40 mL, and 50 mL for 1-5 minutes at each volume and then deflated. Because propagating distal antral contractions sometimes pulled the balloon distally during inflation, catheter movement was restrained if needed using either a rat tooth forceps to grasp the catheter itself or a standard biopsy forceps to grasp a suture affixed to the catheter proximal to the balloon to maintain balloon position stably across the pylorus with continuous endoscopic visualization and visual inspection of the EndoFLIP topographic recording (Medtronic, Minneapolis, MN) during balloon inflation. Data acquired during balloon inflations included pyloric diameter, distensibility, and pressure.

After completion of G-POEM, EndoFLIP text files were uploaded into Excel spreadsheets. Data relating to balloon volume for each of 16 sensors within the EndoFLIP balloon were plotted to identify the sensor(s) which represented the pylorus, as determined by which had the lowest values over the recording segment. For each recording segment, the optimal 40 second segment with the most stable pyloric recording was saved and used for subsequent calculations. This segment was identified by the appearance of a stable diameter decrease along 1-2 pyloric sensors for at least 40 seconds. Using this protocol, we successfully obtained 40 second recordings for 118/120 recording segments (98.3%). The mean + SD time for total inflation from starting inflation to 30 mL to completing the 50 mL inflation was 558+184 seconds and the average time for stable catheter positioning during inflation at each balloon volume was 125+99 seconds. Pyloric data calculated for these 40 second segments for each balloon volume included mean, maximum, and minimum values for diameter and distensibility and mean intraballoon pressure. Variabilities of pyloric diameter and distensibility were calculated by subtracting the minimum from the maximum values for each balloon volume.

Phasic contractions involving the pylorus were defined by transient decreases in pyloric diameter at least 0.25 mm in depth and at least 3 seconds in duration. Three-dimensional contour plots were graphed for each 40 second recording segment using https://plotly.com to permit detailed profiling of phasic contractions involving the pylorus. Pyloric contractions which spanned at least 4 sensors (2 cm) including >2 sensors proximal to the pylorus were considered to originate in the antrum. Additional recording intervals (up to an additional 3 minutes and 20 seconds) not included in these 40 second segments were included to facilitate determination of periods of cycling of repetitive contractions. Additional confirmation of propagating contractions extending through the pylorus was obtained by visual review of topographic videos using the original EndoFLIP topographic recording and FLIP Analytics (initially provided by Crospon, Ltd., Galway, Ireland). Contractions that did not satisfy these criteria were considered to represent other phasic activity. This other activity included single non-repeated contractions propagating from the antrum through the pylorus, individual or repeated contractions isolated to the pylorus (spanning <2 cm), and uncoupled contractions involving the pylorus. Parameters calculated for phasic pyloric contractions included frequencies of cycling (for repeated contractions) and contractile amplitude and duration.

Data Comparisons

Static pyloric EndoFLIP measures (diameter, distensibility, and pressure) were compared before and after G-POEM. Mean values were quantified to assess overall effect of G-POEM on pyloric function; maximum values of diameter and distensibility were assessed to measure impact of G-POEM on maximal pyloric opening while minimum values were assessed to estimate impact of myotomy on pyloric closure. Variability of diameter and distensibility were compared at baseline and after G-POEM. Diameter, distensibility, and pressure were compared during inflation to 30 vs. 40 vs. 50 mL to assess volume dependence of static pyloric EndoFLIP measures.

Pyloric EndoFLIP recordings were characterized as exhibiting (i) phasic, coupled repetitive contractions originating in the antrum, (ii) no phasic contractility, or (iii) other phasic contractions (including single contractions propagating from the antrum, isolated pyloric contractions, and irregular, uncoupled contractions involving the pylorus). The prevalence of each phasic contraction profile was compared before and after G-POEM and with balloon

inflation to 30 vs. 40 vs. 50 mL volume. The impacts of G-POEM and different volumes of EndoFLIP balloon inflation on phasic contractile frequency (for coupled, repeated contractions originating in the antrum), amplitude, and duration were also compared.

Statistical Analyses

All data are expressed as number (n) and percent (%) or mean + standard deviation. Paired two-tailed Student's *t* testing was employed to compare static pyloric parameters (mean, maximum, and minimum values for diameter and distensibility, and mean pressure) before and after G-POEM. Unpaired two-tailed Student's *t* testing was performed to compare means and variability of pyloric diameter and distensibility in relation to the presence vs. absence of phasic pyloric contractions and to compare frequency of repetitive contractions and amplitudes and durations of phasic contractions before and after G-POEM. One-way analysis of variance (ANOVA) compared results of static pyloric parameters as well as frequency of repetitive contractions and amplitudes and durations of phasic contractions between different EndoFLIP balloon volumes (30 vs. 40 vs. 50 mL). Fisher's exact probability tests characterized differences in prevalence of the different phasic contractile profiles (propagated, coupled, repetitive vs. no phasic activity vs. other) before and after G-POEM and in relation to EndoFLIP balloon volumes. Generalized estimating equation (GEE) linear regression models with an autoregressive correlation structure were constructed using the R package *geepack* (v1.2.1) to determine if changes in pyloric diameter and distensibility on EndoFLIP testing occurring after G-POEM were associated with demographic (sex, age, postsurgical vs. diabetic vs. idiopathic etiology), gastric functional (2 and 4 hour scintigraphic retention), clinical (prior vs. no prior botulinum toxin injection, number of prior botulinum toxin injections, days since last botulinum toxin injection), and technical (single vs. double myotomy) factors (25). Statistical significance was defined by P values of < 0.05.

RESULTS

Patient Characteristics

EndoFLIP measurement of static and dynamic pyloric motor activity was performed on 20 patients undergoing G-POEM for refractory gastroparesis. Patients were predominantly

female with a mix of diabetic, idiopathic, and postsurgical etiologies (Table 1). Gastric emptying delays were mostly moderate to severe on scintigraphic testing and three quarters of patients had undergone prior botulinum toxin injection an average of 3.4 times with the last injection session performed an average of 8 months prior to G-POEM. Single pyloromyotomy was performed in 70% of cases and a double myotomy in 30% of cases.

Impact of G-POEM on Static Pyloric Motor Parameters

Static parameters including pyloric diameter, distensibility, and pressure were measured by EndoFLIP under baseline conditions and after G-POEM. Pyloric diameter, distensibility, and pressure showed progressive increases with higher EndoFLIP balloon volumes (Figure 1, Figure 2, and Supplemental Table 1). Mean diameters with EndoFLIP inflation to 40 mL (P=0.0009) and 50 mL (P<0.0001), but not 30 mL, were significantly higher after G-POEM compared to baseline measurements (Figure 1A). Maximum pyloric diameters were higher (P=0.0002) after vs. before G-POEM with EndoFLIP inflation to 50 mL but not lower volumes (Figure 1B). Similarly, mean (P=0.02) and maximum (P=0.02) pyloric distensibility were higher after G-POEM compared to baseline values with EndoFLIP balloon inflation to 50 mL but not lower volumes (Figures 2A, 2B). G-POEM did not affect minimum pyloric diameter or distensibility for any EndoFLIP balloon volume (Figures 1C, 2C). Likewise, G-POEM did not change intraballoon pressures during EndoFLIP inflation to 30 mL, 40 mL, or 50 mL volumes (Supplemental Table 1).

Pyloric diameter and distensibility exhibited significant temporal variability during EndoFLIP balloon inflation. Supplemental Figure 1 shows sample EndoFLIP recordings from a gastroparesis patient prior to G-POEM exhibiting variations in pyloric diameter from a minimum of 13.6 mm to a maximum of 20.0 mm over a 13 second interval. Variability of pyloric diameter was greater after G-POEM compared to before the procedure (P=0.02) with balloon inflation to 50 mL (Figure 3). Likewise, variability of distensibility was higher after G-POEM vs. baseline (P=0.02) at 50 mL volumes (Figure 3).

Dynamic Pyloric Activity Detected by EndoFLIP

Many pyloric EndoFLIP recordings exhibited phasic narrowing of the pyloric lumen. This included phasic contractions which originated in the antrum and propagated in coupled fashion through the pylorus and phasic contractions which were localized to the pylorus as shown in the linear plots from antropyloric sensors and the three-dimensional contour plots from the same recordings in Figure 4. Supplemental Videos 1 and 2 show topographic recordings from two patients who exhibited phasic contractions originating in the antrum and propagating through the pylorus. Other recordings exhibited single coupled contractions from the antrum to the pylorus or uncoordinated phasic activity involving the pylorus (not shown).

Phasic, coupled, repetitive contractions originating in the antrum were noted in 37.5% of recordings and other phasic activity was seen in 23.3%; a lack of phasic contractions involving the pylorus were observed in 39.2% of recordings (Table 2A). Phasic, coupled, repetitive pyloric contractions were observed most often with EndoFLIP balloon inflation to 30 mL and least with 50 mL inflation (P=0.004)(Table 2B). Numbers of phasic, coupled, repetitive contractions trended higher after G-POEM compared to baseline recordings (P=0.051)(Table 2C).

Characteristics of phasic pyloric contractility were compared in relation to EndoFLIP balloon volume before and after G-POEM. Under baseline conditions, the presence of combined phasic pyloric activity (including coupled contractions originating in the antrum and others) was associated with trends to increased variability of pyloric diameter and distensibility at 30 mL and 40 mL balloon volumes (Table 3A). No recordings at 50 mL inflation exhibited phasic activity before G-POEM. After G-POEM, variability of diameter and distensibility was significantly higher in recordings with phasic activity at 40 mL inflation and trended higher with 50 mL inflation (Table 3B). In all recordings overall and in recordings before G-POEM, frequencies of phasic coupled contraction cycling were higher at 30 mL inflation than 40 mL inflation but were similar after G-POEM (Supplemental Table 2A). Phasic coupled contraction amplitudes were similar in relation to balloon volume before and after G-POEM (Supplemental Table 2B). Phasic contractile durations did not relate to balloon volume but were longer for coupled cycling contractions than for other phasic contractions overall (P=0.001) and before G-POEM (P=0.03) but not after G-POEM (P=0.52)(Supplemental Table 2C).

Regression Modeling to Define Predictors of Improved Pyloric Function

Regression models identified potential demographic, clinical, and procedural predictors of improved pyloric function on EndoFLIP testing in patients undergoing G-POEM. Increasing age predicted better improvements in maximum pyloric distensibility (P=0.05), while postsurgical etiology predicted greater overall increases in diameter variability by an average of 2.79 mm relative to diabetic or idiopathic etiology with 50 mL inflation (P=0.02)(Table 4A). Worse 4 hour retention predicted improved distensibility variability at 40 mL inflation (P=0.05). Increasing numbers of botulinum toxin sessions predicted lesser diameter increases (0.36 mm less per session) and distensibility (0.15 mm^2/mmHg less per session) variability at 50 mL (P<0.01)(Table 4B). However, increasing time since the prior botulinum toxin injections predicted better diameter variability increases (0.77 mm higher per 90-day increase) at 50 mL inflation (P=0.03). Other factors exhibiting trends to predicting pyloric response to G-POEM are shown in Tables 4A and 4B.

DISCUSSION

These findings represent the most detailed characterization of pyloric function in gastroparesis at baseline and after G-POEM. Unlike prior EndoFLIP reports, our analyses included comprehensive static and phasic measures which highlight the inherent variability of pyloric function in gastroparesis. Our main aim was to define the impact of endoscopic myotomy on pyloric physiology, our findings provide a foundation to test if expanded EndoFLIP testing can predict outcomes in larger gastroparesis cohorts undergoing pyloric therapy.

We showed overall improved pyloric function after G-POEM including increased mean pyloric diameter and distensibility but not pressure versus pre-myotomy values. This is similar to a prior series which noted distensibility increases after G-POEM and another study which found increased compliance after pyloric dilation (11, 16). Our increases in mean pyloric diameter and distensibility averaged about 2.5 mm and 1.5 mm^2/mmHg after G-POEM, respectively, at 50 mL balloon inflation which are similar to those reported by others (14).

We calculated other measures not previously reported. Increases in maximal EndoFLIP values after G-POEM, including >3 mm dimeter increases and >2 mm^2/mmHg distensibility increases, were numerically greater than for mean values, while G-POEM had insignificant impact on minimum diameter and distensibility. One can speculate that higher maximal

diameters after G-POEM may permit easier evacuation of large, indigestible gastric contents, while the lack of increase in minimal diameters may reflect minimal impact of myotomy on pyloric closure. Studies on the role of the pylorus in regulating gastric emptying have mostly been restricted to healthy animal and human models. Indigestible spheres <1-3 mm in diameter are expelled from the stomach during the fed period, while larger spheres do not empty until fasting patterns resume (26, 27, 28). Pyloric resection or pyloroplasty in dogs does not prevent postprandial sieving, while combined antropyloric excision or combining surgery with vagotomy leads to passage of large undispersed particles suggesting that merely opening the pyloric lumen in health does not permit emptying of poorly triturated chyme (29, 30, 31). Although similar studies have not been conducted in gastroparesis, coupling vagotomy with pyloroplasty may be a suitable animal model for this condition. The functional importance of impaired pyloric sieving is emphasized by studies showing impaired intestinal drug absorption from 3.6 mm versus 0.7 mm pellets (32). The lack of impact on minimal diameter raises the possibility that G-POEM may not adversely increase particle sizes of food residue emptied from the stomach.

Variability of diameter and distensibility served as measures of dynamic pyloric function. Increases in variability of both parameters were seen after G-POEM, likely indicating that myotomy may improve dynamic pyloric motor function in gastroparesis. This may be additional evidence of the beneficial release of "pylorospasm" by the endoscopic technique.

Phasic contractions contributed to some of the diameter and distensibility variabilities. Most phasic activity was comprised of repetitive coupled contractions that originated in the antrum and propagated through the pylorus before diminishing at the duodenal bulb. Frequencies of repetitive phasic contractions were similar to the gastric slow wave. Repetitive coupled contractions were longer in duration compared to isolated and uncoupled contractions. We noted trends to increased repetitive coupled phasic contractions after G-POEM and decreases in numbers of recordings with no phasic contractions after myotomy. This finding contrasts with a study in pigs which noted elimination of distal gastric pressure waves after pylorectomy (33). Research suggests that phasic pyloric contractions are responsive to physiologic stimulation; in pigs, meals increase their amplitude while prokinetic agents increase both their frequency and amplitude (17). The relevance of this phasic activity warrants further study, which will define if these contractile patterns impact gastric emptying rates in gastroparesis or predict better or poorer outcomes after pyloric therapies with G-POEM, surgery, or botulinum toxin.

From a methodologic standpoint, we observed differential utility of EndoFLIP balloon inflation to different volumes. The ability of G-POEM to increase mean and maximum diameter and distensibility and variability of the two measures were only evident at higher volumes, similar to prior reports where responses to pyloric therapies were seen only with 40 or 50 mL inflations (11, 16). In contrast, repetitive coupled phasic contractions were most prevalent at 30 mL volumes and absent phasic activity was most common at 50 mL volumes similar to a porcine study which observed abolition of pyloric motility waves with EndoFLIP inflation to 50 mL (17). The apparent lower frequencies of repetitive contractions with 40 mL versus 30 mL inflation is similar to a study in healthy controls in which antral distention reduced slow wave cycling frequencies by ~50% (34). Although frequencies during 50 mL inflation were higher, very few patients exhibited repetitive contractions at that volume. These findings suggest that performing EndoFLIP testing across a broad range of volumes may be necessary to acquire a comprehensive assessment of pyloric function in gastroparesis.

Our regression analyses provided insight into clinical factors associated with differential pyloric diameter and distensibility responses to G-POEM. We noted superior responses to G-POEM in patients as a function of increasing age. Likewise, outcomes in a large National Institutes of Health (NIH)-supported multicenter gastroparesis cohort were better in those over age 50 suggesting that older patients may exhibit preferential responses to a broad range of gastroparesis therapies (35). Pyloric diameter variability increased more after G-POEM in patients with postsurgical gastroparesis. This etiology typically exhibits more severe gastric emptying impairments and has been a target population for G-POEM at some centers (7, 36, 37). Greater gastric emptying impairments measured by 2- and 4-hour scintigraphic retention showed some association with better responses to G-POEM relating to increased variability of pyloric diameter and distensibility. Of note, the large NIH cohort observed overall better outcomes at 48 weeks in those patients with >20% 4-hour scintigraphic retention (35).

A prominent feature of our cohort was that most patients had undergone prior pyloric botulinum toxin injection to treat gastroparesis. It was the practice of some referring physicians at this site to select only patients for G-POEM who had reported beneficial responses to botulinum toxin. In a large meta-analysis of 332 gastroparesis patients from 11 studies, one predictor of response to G-POEM was prior improvement after pyloric botulinum toxin therapy

(9). It also was typical of our referring physicians to limit the number of botulinum toxin treatments to minimize the risk of scar formation which theoretically could interfere with creating a submucosal tunnel prior to myotomy (38). Scar tissue can develop after lower esophageal sphincter botulinum toxin injection in in achalasia, but has not been confirmed in the pylorus of gastroparesis patients (39). Furthermore, outcomes after Heller myotomy are poorer in achalasia patients who have undergone prior botulinum toxin injection including increased risks of postsurgical dysphagia (40, 41).

Our regression analyses showed uncertain impact of prior botulinum toxin injection. Increases in variability of pyloric diameter and distensibility were lower and increases in maximum distensibility trended lower in those with greater numbers of prior botulinum toxin sessions, but this could be a result of several factors including neurotoxic effects of therapy, preselection of patients with inherently non-variable pyloric function for repeated injections, or progressive scar formation. Increases in time since the most recent botulinum toxin injection were associated with greater increases in diameter variability and trends to larger increases in maximum diameter which could be considered beneficial botulinum toxin effects. However, increased time since the last injection related to trends to lesser increases in mean and maximum distensibility after G-POEM which would be less desirable. These findings do not demonstrate consistent adverse or beneficial effects of repeated botulinum toxin treatment in gastroparesis. In our series, all G-POEM procedures were accomplished successfully without interference by submucosal scar tissue. Definitive characterization of any adverse effects of botulinum toxin on chronic pyloric function in gastroparesis will await similar EndoFLIP analyses from larger gastroparesis cohorts undergoing sequential botulinum toxin injection therapy.

This study had limitations. We conducted predominantly a set of exploratory analyses with the intention of defining effects of endoscopic myotomy on pyloric physiology. This investigation was not designed to define predictors of clinical outcomes of G-POEM. However, we plan to adopt some of the static and dynamic pyloric measures characterized in this study in analyzing a larger multicenter database to determine if EndoFLIP findings can be used to predict improvements in gastric emptying and symptom responses in an outcome study of gastroparesis patients undergoing G-POEM. In particular, our sample size was not large enough to reliably define all clinical and technical factors which relate to improved pyloric function after G-POEM

on regression analyses. However, we believe that some calculations showing statistical significance or trends to significance will inform future analyses of larger databases at our center and possibly external databases generated by others. Three patients were diagnosed using non-standardized scintigraphic criteria, however one patient exhibited abnormal 2 hour scintigraphic retention while two individuals had prior retained food on endoscopy off opioids consistent with a diagnosis of gastroparesis—EndoFLIP findings in these 3 patients were not different from those who were diagnosed using accepted scintigraphy methods (36). Too few patients underwent dual myotomy to assess if this method is superior to single myotomies performed at most centers. Furthermore, patients were not randomized to double versus single myotomy. It would have been desirable to investigate a larger group with postsurgical gastroparesis to better characterize responses to G-POEM given the observed greater pyloric diameter increase observed with this etiology in this initial study. Having EndoFLIP data prior to initial botulinum toxin injection would provide greater detail on physiologic effects of both botulinum toxin and G-POEM on pyloric measures. Finally, we did not have a healthy control cohort to determine if baseline variabilities in pyloric function were blunted in our gastroparesis patients or if improvements in diameter and distensibility after G-POEM restored function into the normal range. Despite these deficiencies, our analyses represent the most comprehensive characterization of pyloric function in gastroparesis before and after G-POEM.

In conclusion, we demonstrated dynamic changes in pyloric activity on EndoFLIP testing in patients with refractory gastroparesis. G-POEM increased mean and maximal diameter and distensibility with associated increases in variability of these parameters, but did not influence minimal values of any parameter. We speculate that endoscopic myotomy enhances pyloric opening but may not impair pyloric closure. Phasic contractions involving the pyloric likely contribute to variations in pyloric diameter and distensibility. It is conceivable that these combined physiologic responses to G-POEM may prove to be advantageous for clinical responses to this therapy. Future studies will determine if these static and dynamic EndoFLIP measures are predictors of response to pyloric therapies such as G-POEM in gastroparesis.

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Specific Author Contributions:

Lydia Watts: Study design, experimental conduct, data collection, data analysis, manuscript preparation, approval of final manuscript version

Jason R. Baker: Study design, experimental conduct, data collection, data analysis, manuscript preparation, approval of final manuscript version

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The authors have no competing interests.

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ABBREVIATIONS

ANOVA—analysis of variance

EndoFLIP—endoscopic functional lumen imaging probe

G-POEM—gastric per-oral endoscopic myotomy

TABLES

Table 1: PATIENT CHARACTERISTICS

Characteristic	Finding
Age	48.8+14.3 years
Sex	15/20 (75%) female
Etiology of gastroparesis	5/20 (25%) diabetic 9/20 (45%) idiopathic 6/20 (30%) postsurgical
Gastric emptying (% retention on scintigraphy)(data available for 17 patients)	65.1+19.4% 2-hour retention 31.4+26.8% 4-hour retention
Prior pyloric botulinum toxin	15/20 (75%) yes
Number of botulinum toxin injection sessions (among patients receiving this therapy)	3.4+2.9
Time since last botulinum toxin injection	245+195 days
G-POEM method	14/20 (70%) single myotomy 6/20 (30%) double myotomy

Table 2: PREVALENCE OF DYNAMIC PYLORIC FUNCTION

Table 2A: OVERALL

Pyloric EndoFLIP Profile	Number (%)

Phasic, coupled contractions from antrum	45/120 (37.5%)
No phasic contractions	47/120 (39.2%)
Other†	28/120 (23.3%)

† Includes isolated pyloric contractions, single contractions propagating from antrum, uncoordinated contractions

Table 2B: RELATION TO ENDOFLIP BALLOON VOLUME

Pyloric EndoFLIP Profile	**EndoFLIP Balloon Volume**			**P Value**
	30 mL Number (%)	**40 mL Number (%)**	**50 ml Number (%)**	
Phasic, coupled contractions from antrum	23/40 (57.5%)	16/40 (40.0%)	6/40 (15%)	0.004
No phasic contractions	5/40 (12.5%)	17/40 (42.5%)	25/40 (62.5%)	<0.0001
Other†	12/40 (30%)	7/40 (17.5%)	9/40 (22.5%)	0.41

† Includes isolated pyloric contractions, single contractions propagating from antrum, uncoordinated contractions

Table 2C: BEFORE AND AFTER G-POEM

Pyloric EndoFLIP Profile	**Before G-POEM Number (%)**	**After G-POEM Number (%)**	**P Value**
Phasic, coupled contractions from antrum	18/60 (30.0%)	27/60 (45.0%)	0.051
No phasic contractions	30/60 (50.0%)	17/60 (28.3%)	
Other†	12/60 (20.0%)	16/60 (26.7%)	

† Includes isolated pyloric contractions, single contractions propagating from antrum, uncoordinated contractions

Table 3: IMPACT OF DYNAMIC FUNCTION ON PYLORIC DIAMETER AND DISTENSIBILITY

Table 3A: BEFORE G-POEM

Parameter	Measure	30 mL EndoFLIP Volume			40 mL EndoFLIP Volume			50 mL EndoFLIP Volume		
		Any Phasic Contractions¶	No Phasic Contractions	P Value	Any Phasic Contractions¶	No Phasic Contractions	P Value	Any Phasic Contractions¶	No Phasic Contractions	P Value
Diameter (mm)	Mean	14.1+2.7	13.0+1.8	0.30	15.5+0.7	13.7+2.0	0.04	--	--	--
	Variability	7.3+5.2	3.1+1.9	0.05	4.8+2.2	2.9+2.6	0.16	--	--	--
Distensibility (mm^2/mmHg)	Mean	8.4+5.0	8.0+3.2	0.84	8.8+4.0	7.4+4.2	0.50	--	--	--
	Variability	8.4+6.7	4.1+4.1	0.12	5.2+2.9	4.0+4.4	0.15	--	--	--

¶ Includes phasic, coupled contractions from antrum, isolated pyloric contractions, single contractions propagating from antrum, uncoordinated contractions

Table 3B: AFTER G-POEM

Parameter	Measure	30 mL EndoFLIP Volume			40 mL EndoFLIP Volume			50 mL EndoFLIP Volume		
		Any Phasic Contractions¶	No Phasic Contractions	P Value	Any Phasic Contractions¶	No Phasic Contractions	P Value	Any Phasic Contractions¶	No Phasic Contractions	P Value
Diameter (mm)	Mean	12.8+3.0	15.9+3.8	0.05	15.7+2.2	15.8+2.9	0.94	19.2+3.5	17.3+1.9	0.13
	Variability	6.6+5.4	5.1+3.9	0.49	6.3+4.1	2.0+1.5	0.006	5.7+4.6	3.2+3.1	0.17
Distensibility	Mean	6.3+3.0	10.4+4.8	0.03	6.8+1.5	10.3+7.5	0.17	7.9+6.6	6.0+1.7	0.33

(mm^2/mmHg)	Variability	6.5+7.3	7.1+6.1	0.86	5.2+2.8	2.8+2.4	0.05	4.7+5.0	2.3+2.5	0.17

¶ Includes phasic, coupled contractions from antrum, isolated pyloric contractions, single contractions propagating from antrum, uncoordinated contractions

Table 4: PREDICTORS OF IMPROVED PYLORIC FUNCTION AFTER G-POEM

Table 4A: DEMOGRAPHIC AND CLINICAL FACTORS

Pyloric Parameter	Potential Predictor	Increase in Pyloric Diameter				Increase in Pyloric Distensibility			
		40 mL Inflation		50 mL Inflation		40 mL Inflation		50 mL Inflation	
		Regression Coefficient (95% CI)	P Value	Regression Coefficient (95% CI)	P Value	Regression Coefficient (95% CI)	P Value	Regression Coefficient (95% CI)	P Value
Mean pyloric parameter	Female sex	-1.34 (-2.86,0.18)	0.08	-1.41 (-2.95, 0.14)	0.07				
	Age (per every 10-year increase)	0.53 (-0.02, 1.08)	0.06	0.49 (-0.02, 1.01)	0.06	0.14 (-0.003, 0.29)	0.06	0.86 (-0.12, 1.84)	0.09
Maximum pyloric parameter	Age (per every 10-year increase)					1.68 (0.01, 3.36)	0.05		
Variability	Age (per every 10-					0.63 (-0.05, 1.32)	0.07		

of pyloric parameter	year increase)								
	Postsurgical etiology (relative to diabetic or idiopathic etiology)			2.79 (0.55, 5.02)	0.02				
	2-hour gastric retention	0.50 (-0.10, 1.10)	0.10					0.40 (-0.06, 0.86)	0.09
	4-hour gastric retention					0.38 (0.01, 0.75)	0.05		

Table 4B: FACTORS RELATED TO PRIOR BOTULINUM TOXIN INJECTION

Pyloric Parameter	**Potential Predictor**	**Increase in Pyloric Diameter**				**Increase in Pyloric Distensibility**			
		40 mL Inflation		**50 mL Inflation**		**40 mL Inflation**		**50 mL Inflation**	
		Regression Coefficient (95% CI)	**P Value**	**Regression Coefficient (95% CI)**	**P Value**	**Regression Coefficient (95% CI)**	**P Value**	**Regression Coefficient (95% CI)**	**P Value**
Mean	Time since last					-0.50 (-1.08, 0.08)	0.09		

pyloric parameter	botulinum toxin session (per every 90 days)								
Maximum pyloric parameter	Number of botulinum toxin sessions (per every 1 session increase)							-0.20 (-0.42, 0.03)	0.09
	Time since last botulinum toxin session (per every 90 days)			0.69 (-0.13, 1.51)	0.10	-0.77 (-1.67, 0.14)	0.10		
Variability of pyloric parameter	Number of botulinum toxin sessions (per every 1 session increase)			-0.36 (-0.65, -0.08)	0.01			-0.15 (-0.26, -0.04)	0.007
	Time since last botulinum toxin session (per every 90 days)	0.51 (-0.04, 1.07)	0.07	0.77 (0.09, 1.45)	0.03				

FIGURE LEGENDS

Figure 1: This figure shows the impact of G-POEM (gray bars) compared to baseline recordings (clear bars) on pyloric diameter measured by EndoFLIP balloon inflation to different volumes. G-POEM resulted in significant increases in mean pyloric diameter with 40 mL and 50 mL inflation (A) and significant increases in maximum pyloric diameter with 50 mL inflation (B), but did not significantly change minimum diameter (C).

Figure 2: This figure shows the impact of G-POEM (gray bars) compared to baseline recordings (clear bars) on pyloric distensibility measured by EndoFLIP balloon inflation to different volumes. G-POEM resulted in significant increases in mean pyloric distensibility (A) and maximum pyloric distensibility (B) with 50 mL inflation, but did not significantly change minimum distensibility (C).

Figure 3: This figure shows the impact of G-POEM (gray bars) compared to baseline recordings (clear bars) on variability of pyloric parameters. G-POEM resulted in significant increases in variability of both pyloric diameter (A) and distensibility (B) with 50 mL inflation.

Figure 4: These plots display the different profiles of pyloric function during EndoFLIP recording. The tracings on the left show linear diameter readings as a function of time from individual sensors positioned in the pylorus (blue) and antrum from 0.5 to 3 cm proximal to the pylorus (red). Three dimensional contour plots shown in the right graphs which are generated to profile diameter responses across all sensors in the antrum, pylorus, and duodenum. The top plots show propagating contractions originating in the antrum and migrating through the pylorus leading to diameter reductions in the antrum followed by the pylorus. Dashed lines on the linear plot show antegrade propagation of these contractions. In the middle plots, a single intense contraction isolated to the pylorus and the most distal 1 cm of antrum at 15 seconds into the recording is shown. The bottom plots show a recording without phasic contractions which exhibit a stable pyloric diameter.

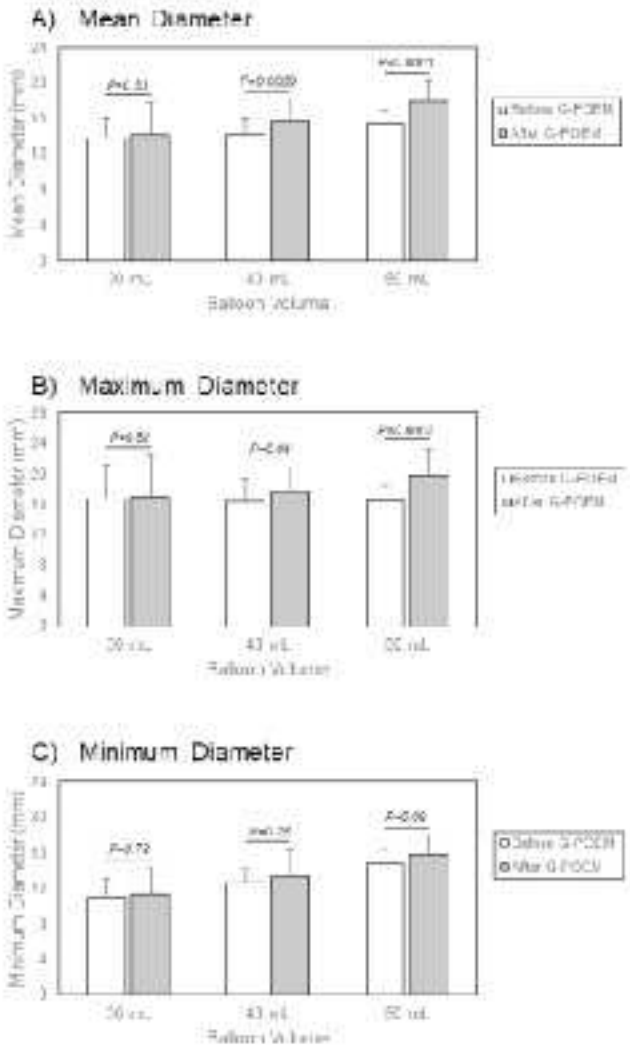

Figure 1

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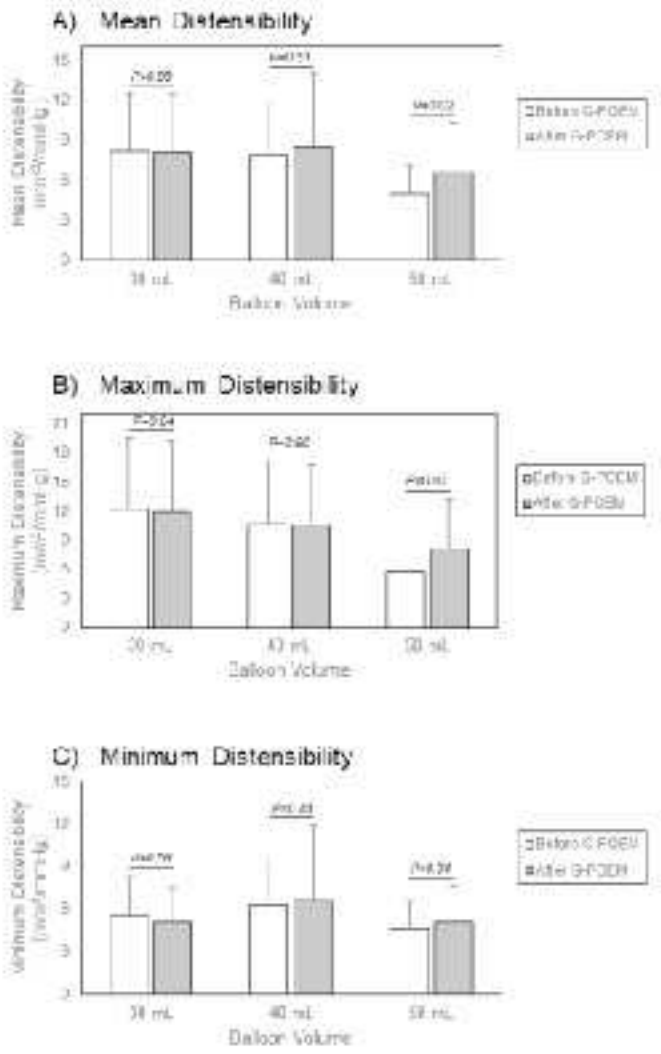

Figure 2

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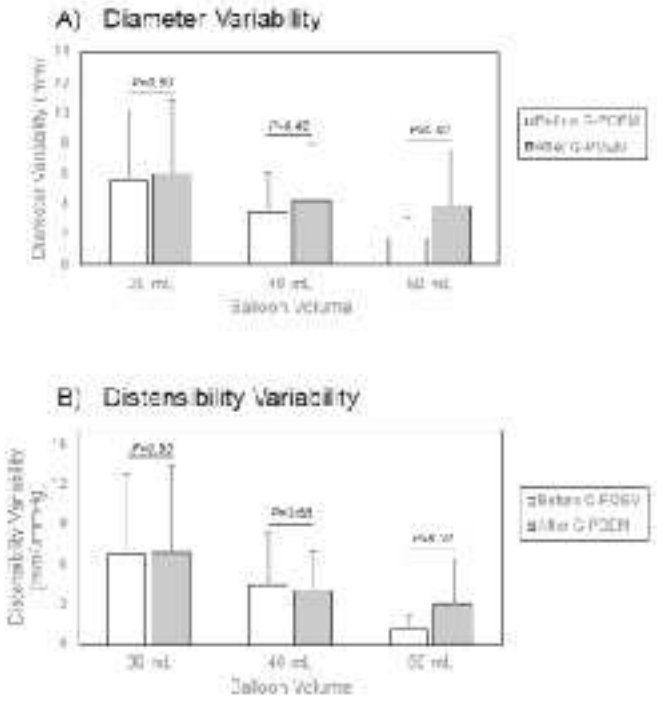

Figure 3

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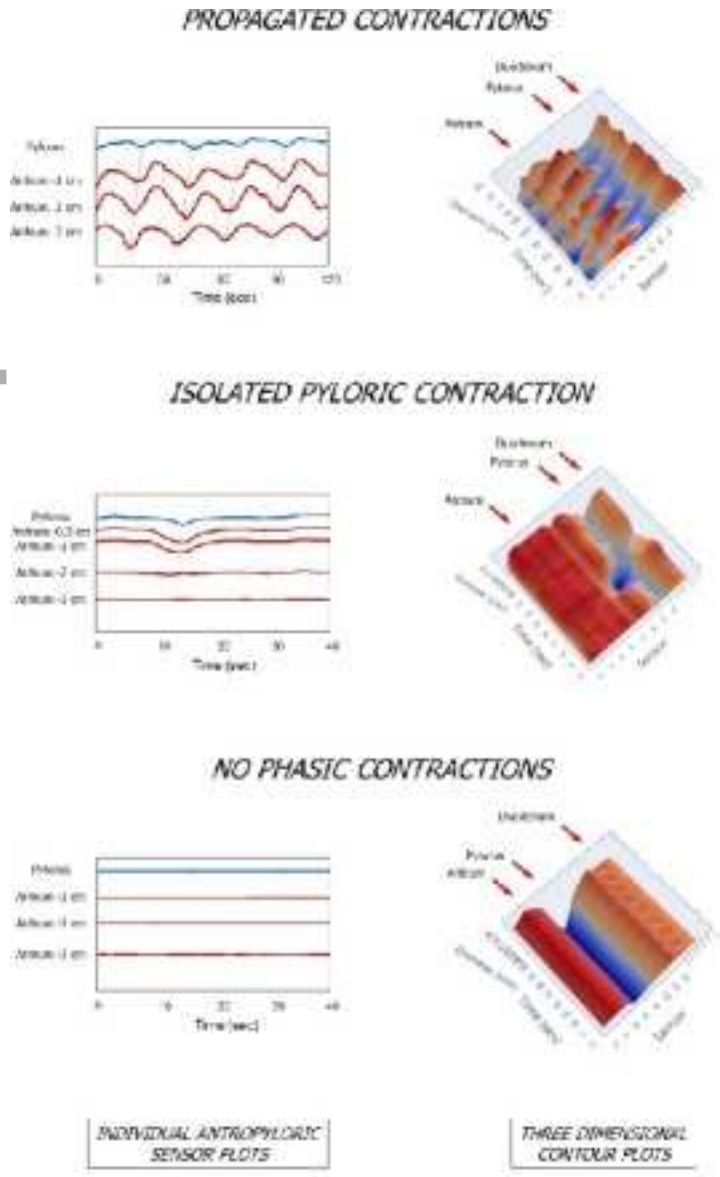

Figure 4

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