What's Moving in GI Motility & Irritable Bowel Syndrome (IBS)

Highlights from DDW 2014

Henry P. Parkman, MD
Professor of Medicine
Director of GI Motility Laboratory
Gastroenterology Section
Temple University School of Medicine
Philadelphia, PA

Disclosure of Conflicts of Interest

- **Henry P. Parkman, MD,** has affiliations with GlaxoSmithKline (GSK), Therapuetic Inc., Evotec (*Grant*).

Esophageal Motility Disorders

POEMS for achalasia

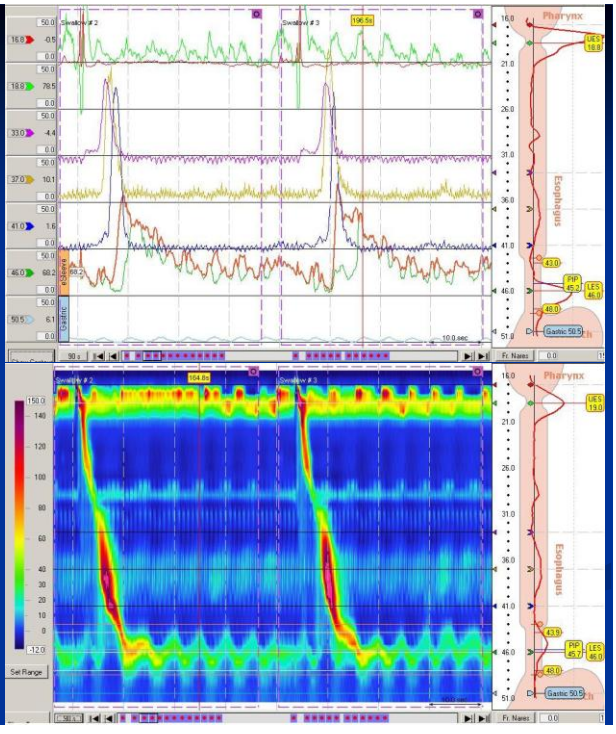
EGJ Outflow Obstruction

Use of EndoFlip to assess LES compliance

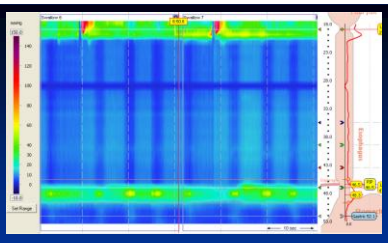
Use of impedance during esophageal manometry

High Resolution Manometry

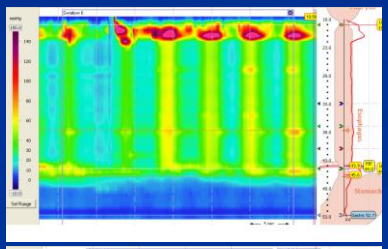
Normal Subject



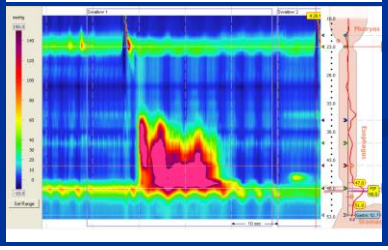
Achalasia Type 1



Achalasia Type 2



Achalasia Type 3



Peroral Esophageal Myotomy (POEM) for Achalasia

Inoue series. 500 POEM Cases. Overall success rate of 94.7% (Eckerdt score<3). Durable out to 3 years. Symptomatic GERD in 16%.

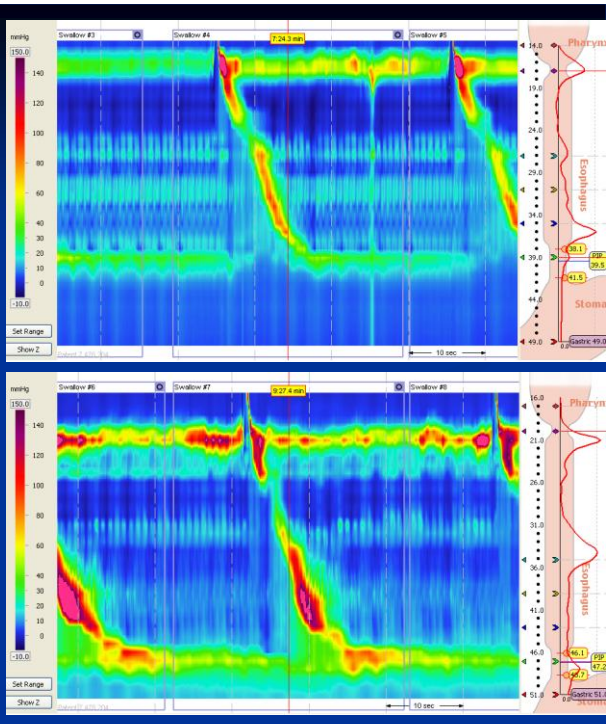
Kumbhari, Stavropoulas et al. POEM compared to retrospective series of Lap Heller for Type III Achalasia: 100% response for POEM compared to 80% for Lap Heller.

Familiari et al. POEM for Achalasia. 119 patients. Successful in 94.9%. Eckerdt score decreased from 7.0 to 1.0 at 12 months. LESP decreased from 40 to 18 mmHg. GERD present by testing in 45.8%; Erosive esophagitis in 25%.

Khashab at Johns Hopkins. 26 patients. POEM can be effectively and safely performed by experienced gastroenterologist in a tertiary care endoscopy unit. The learning curve for POEM is 13 cases.

Normal
normal EGJ relaxation
intact peristalsis

Esophagogastric Junction Outflow Obstruction (EGJOO)
impaired EGJ relaxation
intact peristalsis



What is the Clinical Significance of EGJ Outflow Obstruction?

Okeke FC, Raja S, …, Pasricha PJ, Clarke JO. Gastroenterology 2014,

60 patients met criteria for EGJOO.

Dysphagia was the most common presenting symptom (n=34).

22 underwent intervention. Persistent improvement was seen in only 1 of 9 patients who underwent dilatation, 1 of 6 patients who underwent botulinum toxin and all 3 patients who underwent per-oral endoscopic myotomy (POEM). No patients treated with medical therapy alone had improvement in dysphagia.

Conclusion: The manometric criterion EJGOO defines a **heterogeneous clinical group**. Our early data suggest that for patients with dysphagia, outcome may depend on **EGJ disruption**, with POEM being most successful treatment.

Measurement of Esophagogastric Junction Distensibility Identifies a Subgroup of Achalasia Patients With Manometrically Normal LES Relaxation.

Fraukje A. Ponds, Albert J. Bredenoord, O. Rohof, Jac. Oors, André J. Smout

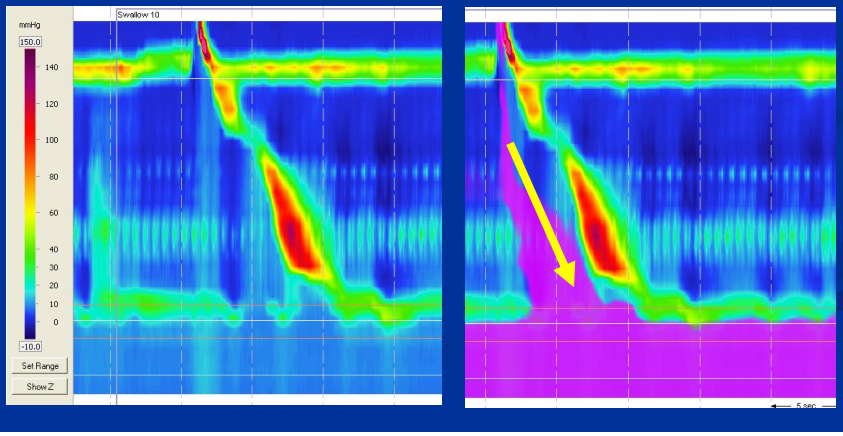
Consecutive patients with typical symptoms of achalasia, significant stasis on barium esophagogram, absent peristalsis on manometry but normal IRP were included. Impedance planimetry (**EndoFLIP)** was used to measure distensibility of the EGJ.

12 patients (5 male; age 21-59 years) with typical symptoms of achalasia and an Eckardt score of 6.5 (5-7) (median (IQR)). Esophageal manometry showed absent peristalsis (7 type I, 2 type II, 3 type III) with a median IRP4 of 9.3 (5.7-12.5) mmHg and baseline LES pressure of 9.3 (5.4-13.2) mmHg. The barium esophagogram showed stasis of 7.2 (5.2-11) cm. Distensibility of the EGJ was significantly reduced in patients compared to healthy subjects at larger balloon volumes. **All patients exhibited EGJ distensibility below the lowest value observed in healthy subjects.** Treatment performed in 11 patients (8 pneumodilation, 3 Heller myotomy). Post-treatment, the Eckardt score was significantly reduced (2 (1-3.3) p <.05) in 10 patients.

A subgroup of patients with typical features of achalasia but manometrically normal LES relaxation has impaired EGJ distensibility at impedance planimetry. These patients respond favorably to achalasia treatment. There is a subgroup of patients with achalasia whose impaired LES relaxation cannot be identified manometrically.

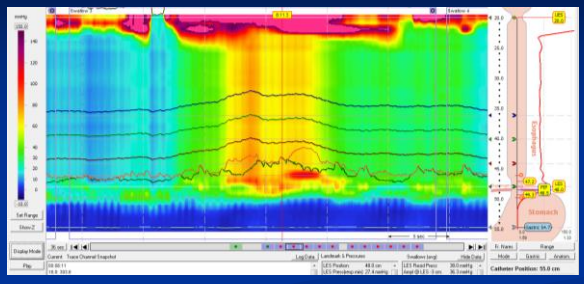
Evaluation of Bolus Transit

- Gold Standard: Barium Video Esophagram
- Addition of Esophageal Impedance to Manometry

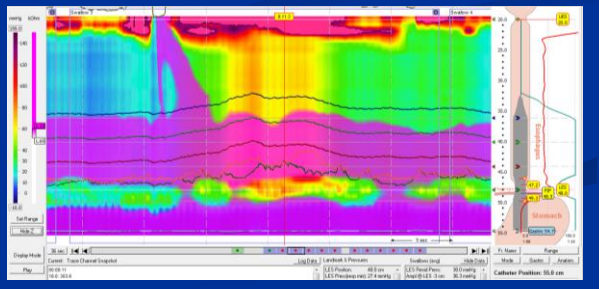


Achalasia: Manometry and Impedance

HREM



HREMI



Novel Impedance Measurements to Assess Bolus Retention in Achalasia

Elyse R. Johnston, …, Peter J. Kahrilas, John E. Pandolfino

The aim was to develop new techniques to assess bolus retention in achalasia using high resolution impedance manometry (HRIM).

20 achalasia patients were evaluated with HRIM utilizing a 200 ml saline challenge protocol in upright position. These patients underwent a timed barium esophagram (TBE) within 1 month using 200 ml barium. A metric to simulate bolus retention on TBE was created by determining the **impedance bolus height (IBH)** at 30 second time intervals along the 5 minute protocol.

The correlation between the color impedance topography method and the spatial impedance variation plot approach for measuring IBH was excellent at both the 1 minute (R=0.99) and the 5 minute (R=0.99) time point. The correlation between the symptom IDQ score and the three metrics developed using impedance to assess bolus retention in achalasia were similar to barium column at 5 minutes on TBE (IBH at 5 minutes- IDQ, R=0.40; IBA-IDQ, R=0.48; ½ time IBHIDQ,R=0.40; TBE at 5 minutes-IDQ, R=0.35).

HRIM can be leveraged to visualize and assess bolus retention dynamics in achalasia similar to the standard TBE protocol. These metrics have fair correlation with symptom severity. Future studies should focus on if these tools can predict outcome in achalasia.

Gastroparesis and Functional Dyspepsia

Outcome

Treatments

Morbidity, Mortality Predictors of Improvement in Patient s with Gastroparesis: 4-Year Outcomes form the Gastroparesis Clinical Research Consortium.

Pasricha PJ, Yates KP, Clarke JO, et al. Gastroenterology 2014, A-224

358 patients with gastroparesis (73% Delayed GE, 27% Normal GE)

70% idiopathic, 14% T1DM, 16% T2DM

Overall, GCSI decreased by 0.41 at 48 week follow up

Only 28% of patients had decrease in GCSI >1

Predictors of improvement in patients with DGE (gastroaparesis):

- older age
- less severe abdominal pain
- normal, rather then high, BMI
- less depression, anxiety
- initial infectious prodrome

Conclusions: Most patients with gastroparesis do not improve over time.

The disease burden of gastroparesis remains high.

Treatments for Gastroparesis Reported at DDW 2014

Prokinetic Agents

Intranasal metoclopramide for diabetic gastroparesis. Phase IIb study:

reduced symptoms in females, but not males

Audience: In Europe, metoclopramide for 5 days; domperidone 10 mg TID for 7 days

Camicinal, a motilin receptor agonist in diabetic gastroparesis. Phase II

High doses (125 mg) enhanced gastric emptying

Lower doses (10, 50 mg) improved symptoms, particularly fullness; but did not affect gastric emptying

RM-311, a ghrelin receptor agonist in diabetic gastroparesis. Phase II

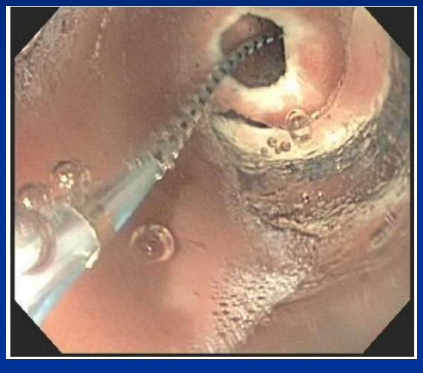
Improved gastric emptying and decreased vomiting

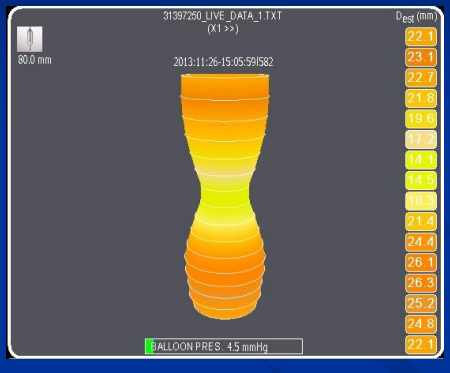
Antiemetics

Granisetron patch, a 5-HT3 receptor antagonist. Investigator-initiated study.

Improved symptoms of nausea, vomiting, but also early satiety, fullness

EndoFlip of Pyloric Sphincter





Measure of Fasting Pyloric Pressure and Compliance in Gastroparesis

Gourerol G, Tisster F, et al. Gastroenterology 2014, A-392

Fasting pyloric pressure and compliance was investigated in 21 healthy volunteers (HV), 17 gastroparetic patients (GP; diabetic: n=2; post-surgical: n=2; idiopathic: n=13). Pyloric compliance was measured using the EndoFLIP® technique (with balloon inflated at 40 ml).

Fasting pyloric pressure increased in GP (14.2±1.5 mmHg) compared to HV (9.6±1.0; $p<0.05$).

Pyloric pressure did not correlate with T1/2 in GP.

Pyloric compliance was decreased in GP (13.9±2.43.0 mm2/mmHg; $p<0.01$) compared to HV (25.2±2.4 mm2/mmHg).

In GP, fasting pyloric compliance correlated negatively with T1/2 (R= -0.44; $p=0.04$).

Six GP with low (<10 mm2/mmHg) fasting pyloric compliance underwent hydraulic dilation (20 mm) of the pylorus. One week after pyloric dilation, fasting pyloric compliance was increased in all patients from 7.7 to 22.8 mm2/mmHg ($p=0.03$). After dilation, T1/2 accelerated in 5/6 patients while quality of life improved in 4/6 patients.

Conclusion: This study assessed the pyloric compliance, and showed that fasting pyloric compliance is decreased in GP. Fasting pyloric compliance, but not fasting pyloric pressure, was negatively correlated with T1/2, suggesting that pyloric compliance is a key determinant in gastric emptying rate. No specific symptomatic pattern was observed among GP with decreased or normal pyloric compliance.

Endoscopic Pyloromyotomy through a Gastric Submucosal Tunnel Dissection for the Treatment of Gastroparesis After Surgical Vagal Lesion

Chaves DM, de Moura EG, et al. Gastroenterology 2014.

The technique presented in the video shows an endoscopic pyloromyotomy, through a submucosal gastric tunnel dissection, preserving an intact serosa and maintaining the mucosal layer at the pyloric channel.

Endoscopic pyloromyotomy was performed. After the pylorus identification, 2cm proximal to it, in the greater curvature of the stomach, a gastric submucosal space was tunneled up to the pylorus, using the following technique:

A) Injection of the Methylene blue with saline solution in the submucosal to elevate it;

B) Mucosal incision (1.5cm) to create entry to submucosal space, employing Flushknife;

C) Dissection of the submucosal until identifying the pyloric muscle;

D) Complete section of the pyloric muscle, keeping intact the adjacent serosa;

E) Closure of the gastric tunneling with metallic clips.

The patient had very good increase in her quality of life.

This technique is feasible, easy to perform, and may be alternative to pyloroplasty in selected cases.

Functional GI Disorders: Rome IV

Disorders of GI function in the absence of structural disease.

A new working definition for functional GI disorders. :

Disorders of Gut-Brain Interactions:

A group of disorders classified by GI symptoms related to any combination of:

- Motility disturbance
- Visceral hypersensitivity
- Altered mucosal and immune function
- Altered gut microbiota
- Altered CNS processing

GI Bowel Symptom Comorbidity in Functional Dyspepsia: The Functional Dyspepsia Treatment Trial (FDTT).

Saito YA, Almazar AE, Locke GR, et al. Gastroenterology 2014, A-288

Treatment Response in Functional Dyspepsia (reported in DDW 2013)

Placebo	40%
TCA: Amitriptyline 50 mg	53%; p=0.05
SSRI: Escitalopramine (Lexapro) 10 mg	38%

Overlap of IBS and FD:

21% of FD also meet IBS criteria:

(41% IBS-C, 33% IBS-D, 10% IBS-M, 18% undifferentiated IBS)

generally dysmotility-like FD

Treatment response with antidepressants did not differ between FD and FD-IBS, suggesting the presence of additional GI symptoms does not decrease the likelihood of response to antidepressant therapy.

Treatments for IBS reported at DDW 2014

IBS-D

Eluxadoline, a locally active, mixed mu opioid receptor agonist and delta opioid receptor antagonist.

Phase III study.

Favorably reduced symptoms

IBS-D

Mesalazine (mesalamine) not helpful

IBS

Mesalazine not helpful

Treatments for Chronic Constipation reported at DDW 2014

Prucalopride, a 5-HT4 agonist.

Phase III study multicenter, randomized controlled study in men: prucalopride 2 mg per day versus placebo.

Primary endpoint: proportion of patients achieving a mean of >3 SCBMs per week

Prucalopride	37.9% ($p<0.001$)
Placebo	17.7%

Adverse events: Diarrhea 6.5%, Nausea 6.0%, Headache 9.2%, Abdominal pain 4.3%

Positive benefit-risk profile in the use of prucalopride in men with chronic constipation.

Effects of Low-FODMAP and Gluten-Free Diets in Irritable Bowel Syndrome Patients. A Double-Blind Randomized Controlled Clinical Study

Daria Piacentino, Sara Rossi, Valeria Alvino, Rosanna Cantarini, Danilo Badiali, Nadia Pallotta, Enrico Corazziari

There is increasing evidence of efficacy of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) for the treatment of IBS. Non-celiac patients with IBS-like symptoms may benefit of a gluten-free diet, being indicative of non-celiac gluten sensitivity (NCGS). Overlap between IBS and NCGS is frequent.

To assess in IBS patients the effect on bloating, abdominal distension, and abdominal pain of three types of diet: 1) low FODMAP and gluten-free (FOD-GF); 2) low-FODMAP and normal-gluten (FOD-NG); 3) normal-FODMAP and normal-gluten (controls).

60 IBS outpatients (F=37, age range=21-67 years) were randomly and blindly assigned to one of the three dietary protocols (20 patients to each), which they followed for 4 weeks.

FOD-NG and FOD-GF groups showed a significant improvement of bloating, abdominal distension, and pain. A greater improvement of IBS symptoms in the two test diet groups vs. the controls, and trend favoring the FOD-NG group vs. FOD-GF group.

IBS patients have considerable benefit of restricting FODMAPs in the diet. Gluten avoidance in addition to a FODMAP restricted diet does not seem to add any significant benefit.

Validating a Biomarker for Irritable Bowel Syndrome

Michael Camilleri, Andrea Shin, Irene A. Busciglio, Duane D. Burton, Alan R. Zinsmeister

Aim: To characterize bile acid (BA) measurements, colonic transit and intestinal and colonic permeability in three groups of participants: IBS- diarrhea (IBS-D), IBS- constipation (IBS-C) and healthy volunteers (HV); and to develop a model that can be used as a biomarker to differentiate IBS from health.

Results: There were expected differences in IBS-C, IBS-D and HV groups in CT (GC 24h and 48h), small intestinal permeability, fecal fat, serum FGF19 and C4, and total fecal BA. A 3-variable model that included total fecal BA, colonic transit at 48h, and a measure of small bowel permeability showed: (a) **total fecal BA** was an independent predictor for HV vs. IBS-D, and IBS-C vs. IBS-D; (b) **GC48** was significant in discriminating HV from IBS-C, and IBS-C from IBS-D. Serum C4 and FGF19 measurements did not provide additional discrimination to total fecal BA. Small intestinal permeability was not an independent predictor. At 80% sensitivity, the 3-variable model had 43% specificity to differentiate IBS-D from HV, 57% specificity for IBS-C from HV, and 81% specificity to differentiate IBS-C and IBS-D. For the latter differentiation, there was 63% specificity at 90% sensitivity.

Conclusion: The differences in quantitative traits between the three groups and the multiple-variable model suggest that combination of **colonic transit** plus **fecal total BA** constitutes a useful combination biomarker for identifying or differentiating IBS-C and IBS-D.

What's Moving in GI Motility & Irritable Bowel Syndrome (IBS)

Esophagus: Achalasia

Stomach: Gastroparesis and Functional Dyspepsia

Colon: Irritable Bowel Syndrome and Chronic Constipation

Effects of the Herbal Drug STW 5 and Its Individual Components on Human Intestinal Motility

Shady Allam, Dagmar Krueger, Michael Schemann.. Gastroenterology 2014, 388

STW5 (Iberogast) consists of hydroethanolic extracts from iberis amara, chamomile, peppermint, caraway, liquorice, lemon balm, angelica, greater celandine and milk thistle and is clinically used to treat functional gut disorders.

We studied the so far unknown effects of STW5 and its components on human intestinal motility.

Methods: In vitro motility effects of STW5 were studied in 575 circular (CM) or longitudinal muscle (LM) strip preparations of human small or large intestinal specimens from 114 patients undergoing abdominal surgery. Parameters were tonic contractions (muscle tone, MT) and phasic contractions (Motility index, MI).

Results: STW5 significantly and dose dependently reduced MT. Effects were more predominant in large vs. small intestine and in CM vs. LM. STW5 had region-specific effects on MI reduction of duodenum and jejunum. Both regions showed comparable reduction in MT. In large intestinal CM; MI was transiently increased followed by a complete inhibition of phasic contractility. Reduction in MT was significantly higher in large than in small intestine. In small intestine, all extracts (except milk thistle and iberis amara) reduced MT and MI. In large intestine, peppermint, liquorice and angelica reduced MT and MI, thereby mimicking STW5 actions. Additionally, caraway and lemon balm decreased MT while G.celandine increased it.

Conclusion: STW5 has region- and layer-specific activities in the human intestine.

Apart from milk thistle and iberis amara, all extracts contributed to the effects of STW5.

Peppermint, angelica and liquorice mimicked its inhibitory action on muscle activity.

The identification of region and target specific actions of STW5 and its components suggests their potential for treating small and large intestinal motility disorders.

Questions?