Esophageal Function Testing: State of the Art

John E. Pandolfino, MD, MSCI
Hans Popper Professor of Medicine
Feinberg School of Medicine,
Northwestern University
Chief, Division of Gastroenterology and Hepatology
Northwestern Medicine
Northwestern Memorial Hospital

Esophageal Function Testing
State of the Art

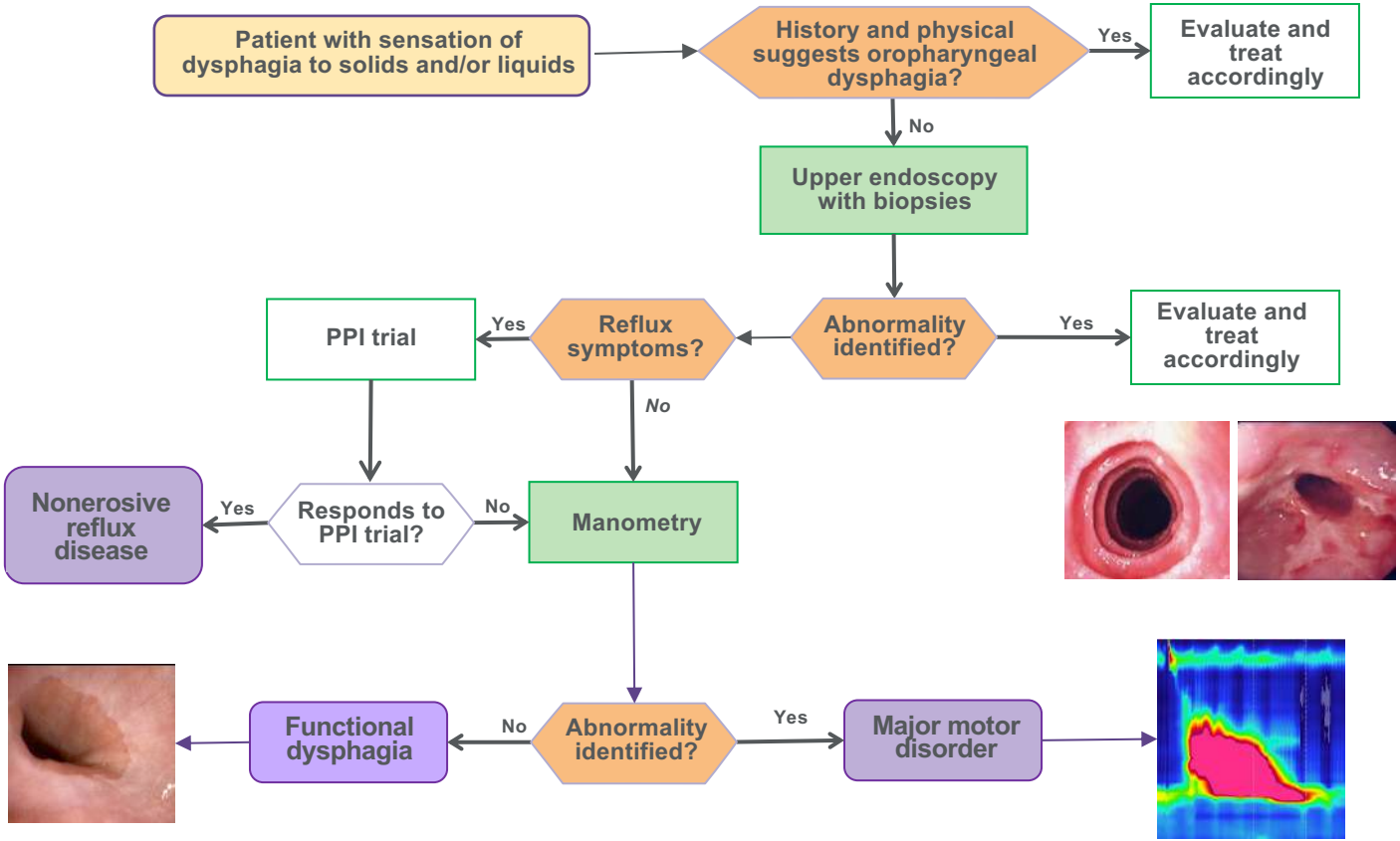
- Discuss important technological advances in esophageal function testing focused on dysphagia.
  - CC 4.0
  - CC 5.0- Impedance
  - FLIP-Panometry
  - In-silico modeling and machine learning

Esophageal Symptoms
Diagnostic Approach

- Heartburn, regurgitation, dysphagia, chest pain and food impaction.
- Differential Diagnosis:
  - *GERD, EoE, Obstruction, Motor Disorder, Functional Esophageal Disorder*

- All roads lead to endoscopy
  - r/o mechanical obstruction, reflux injury, EoE
  - Negative- NERD, motility disorder, functional

Rome IV Diagnostic algorithm: Dysphagia

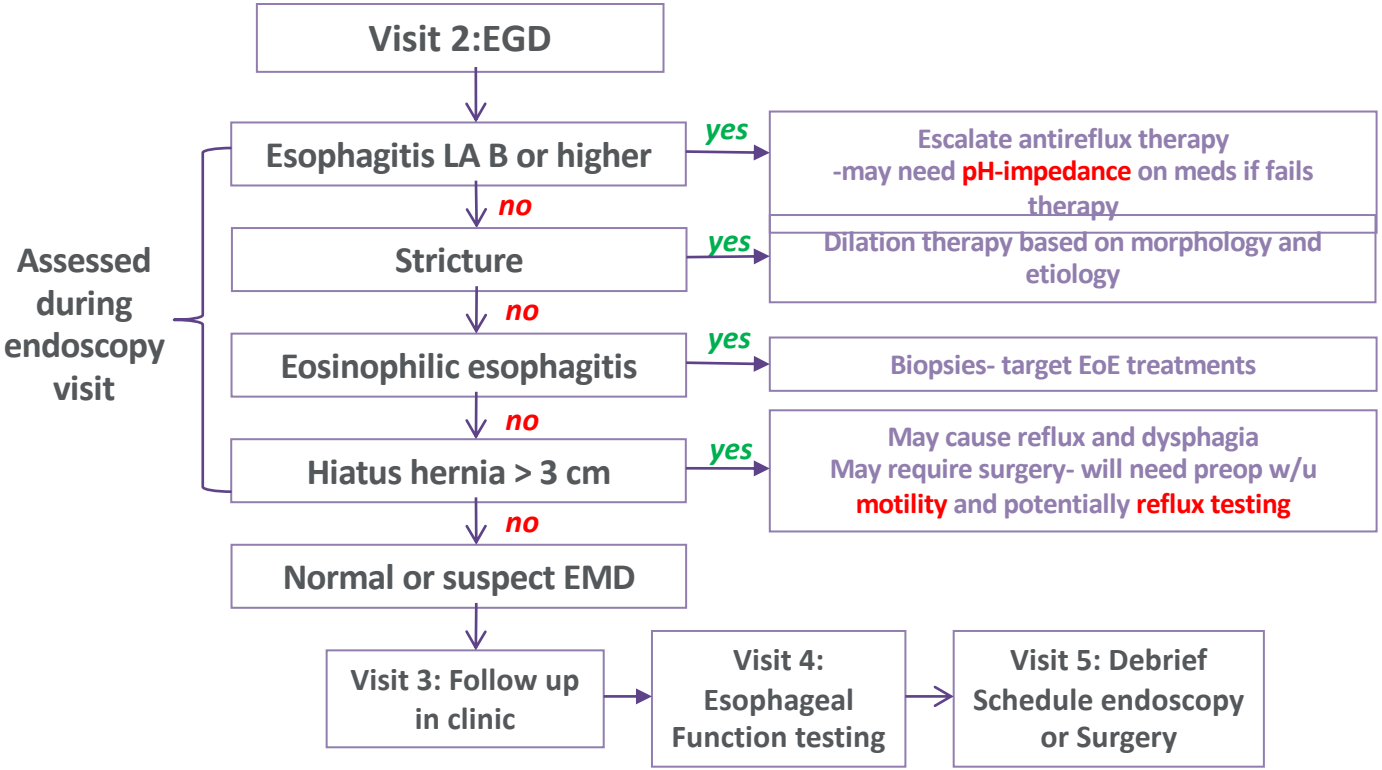


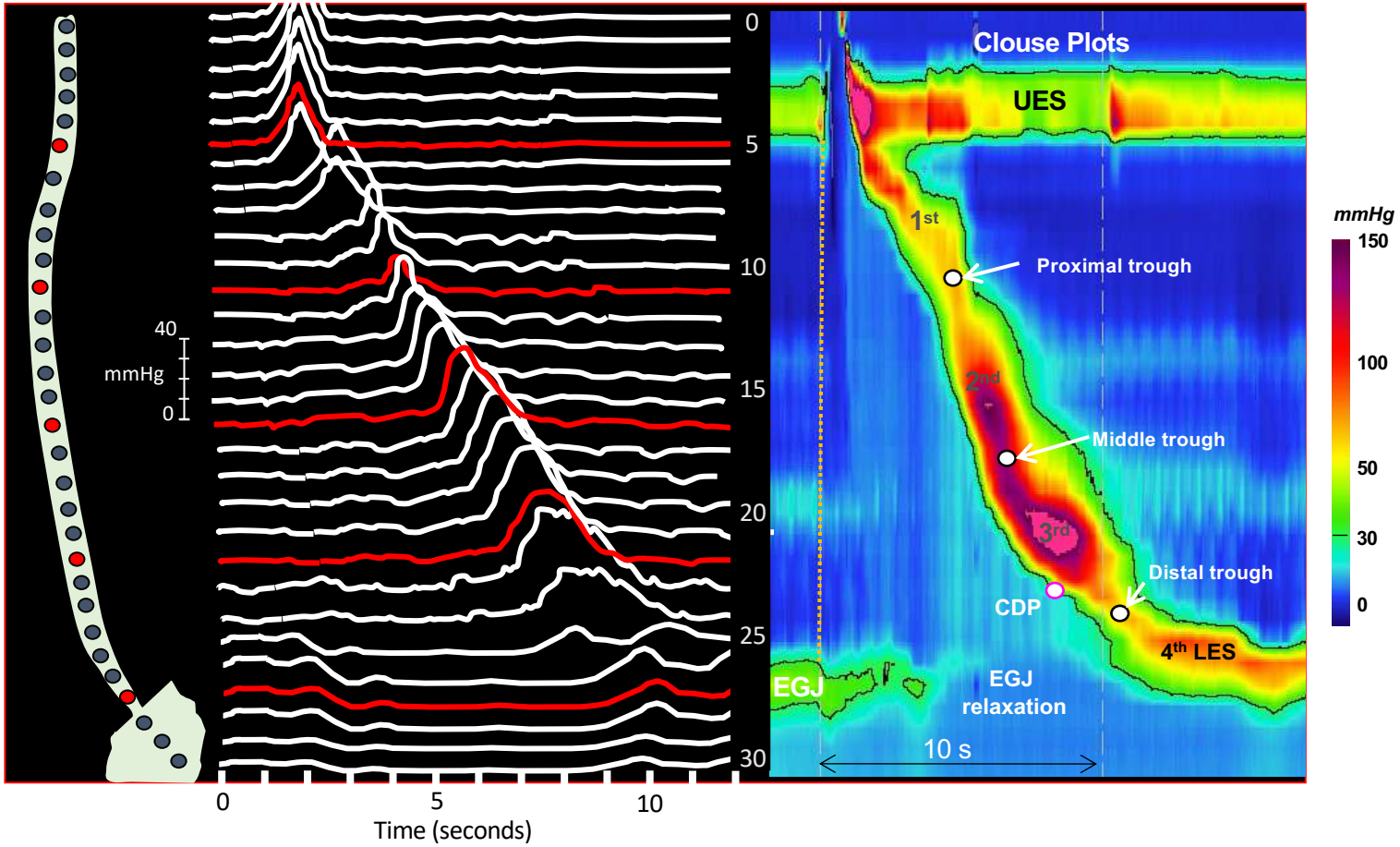
Approach to patient with esophageal complaints:

-Dysphagia, Regurgitation, Chest pain, Food impactions

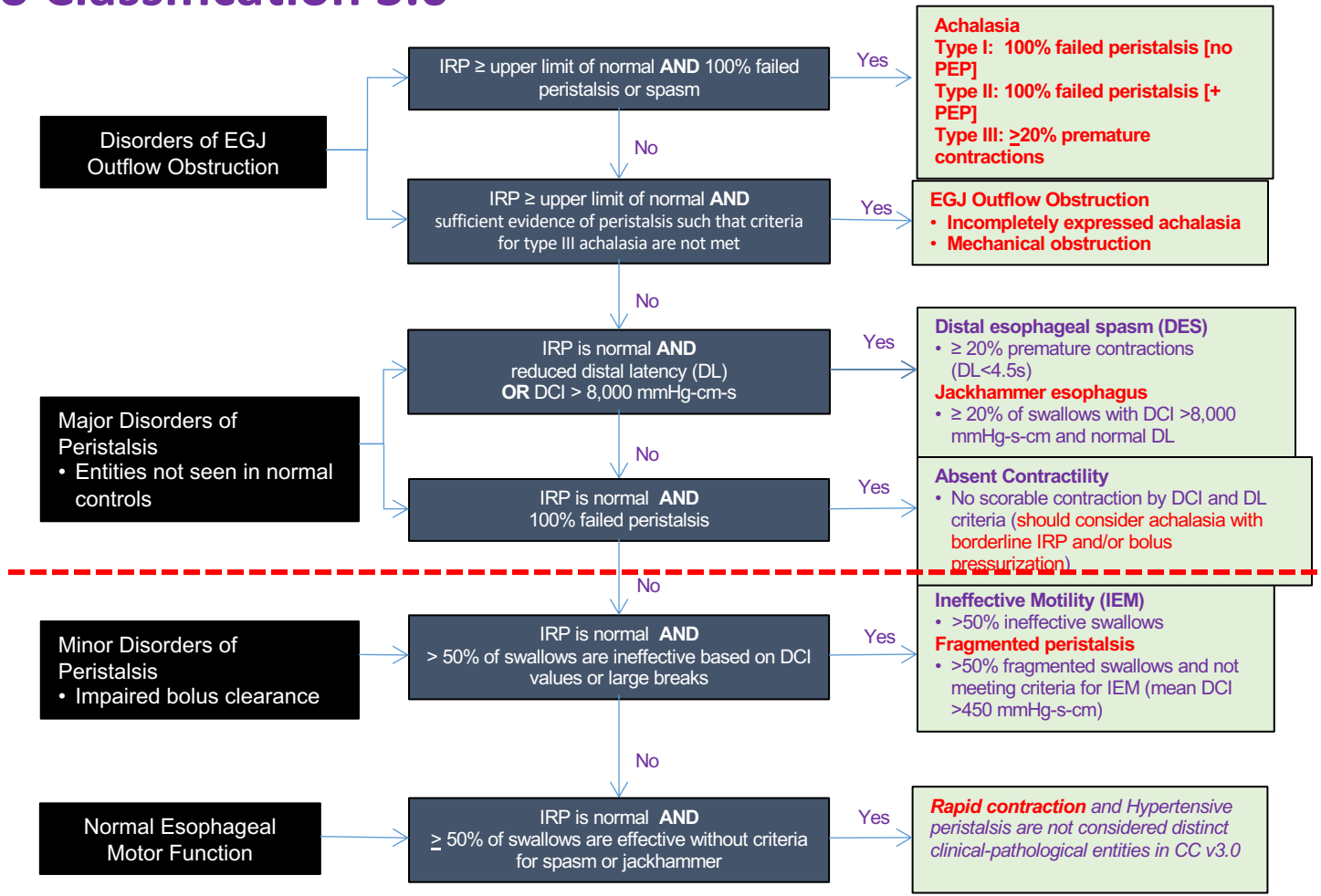
-Diff Dx: GERD, EoE, EMD/Achalasia- difficult to distinguish on history

Visit 1: potentially prescribe a 4-8 week course of PPI and schedule endoscopy




Catheter Configuration
Line Plots (pressure vs time) of Conventional and High Resolution Manometry
HRM Plotted in Esophageal Pressure Topography
40
mmHg
0
0
5
10
15
20
25
30
Time (seconds)
Clouse Plots
UES
1st
Proximal trough
2nd
Middle trough
3rd
Distal trough
CDP
4th LES
EGJ
EGJ relaxation
10 s
mmHg
150
100
50
30
0

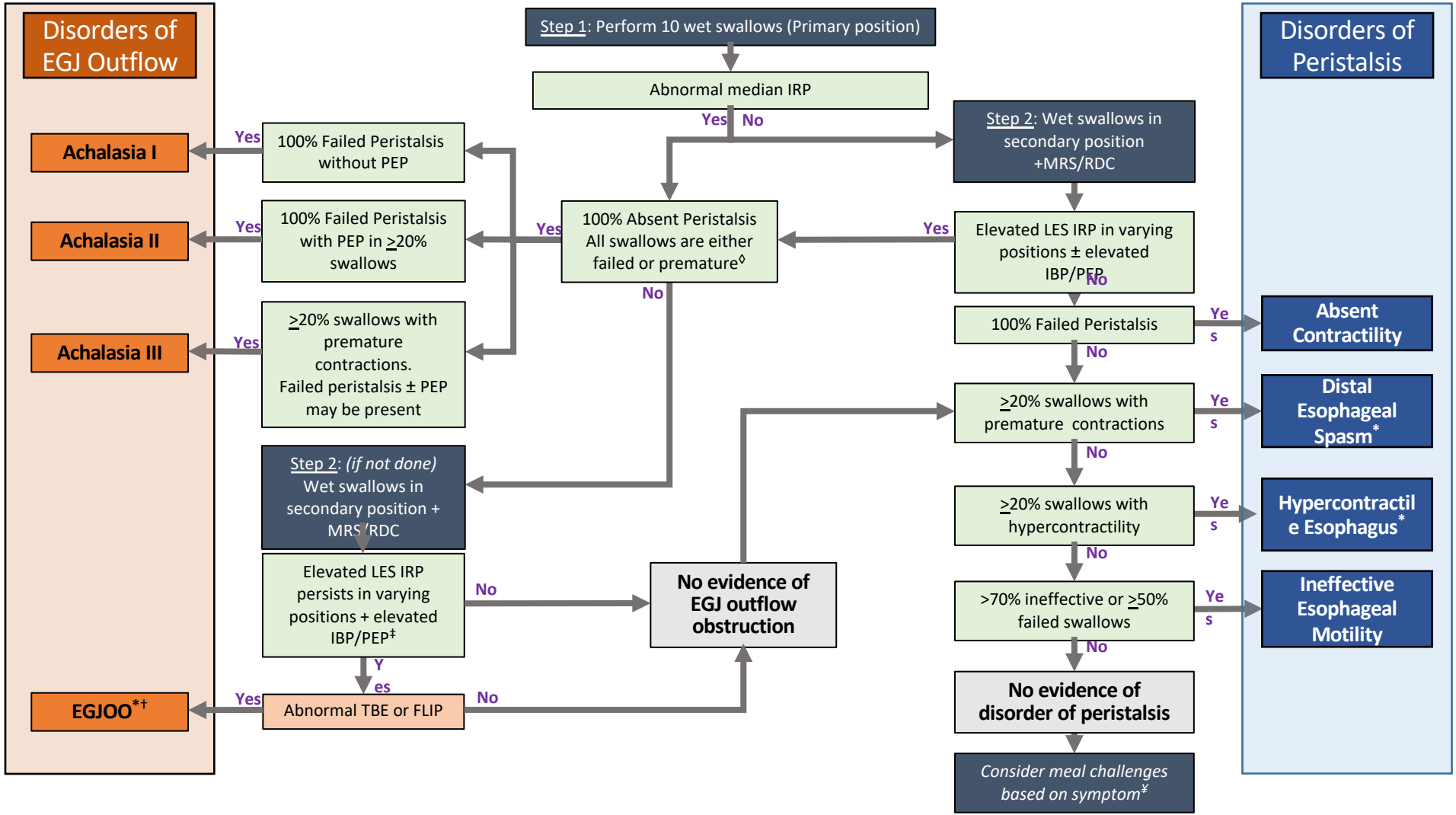
Chicago Classification 3.0



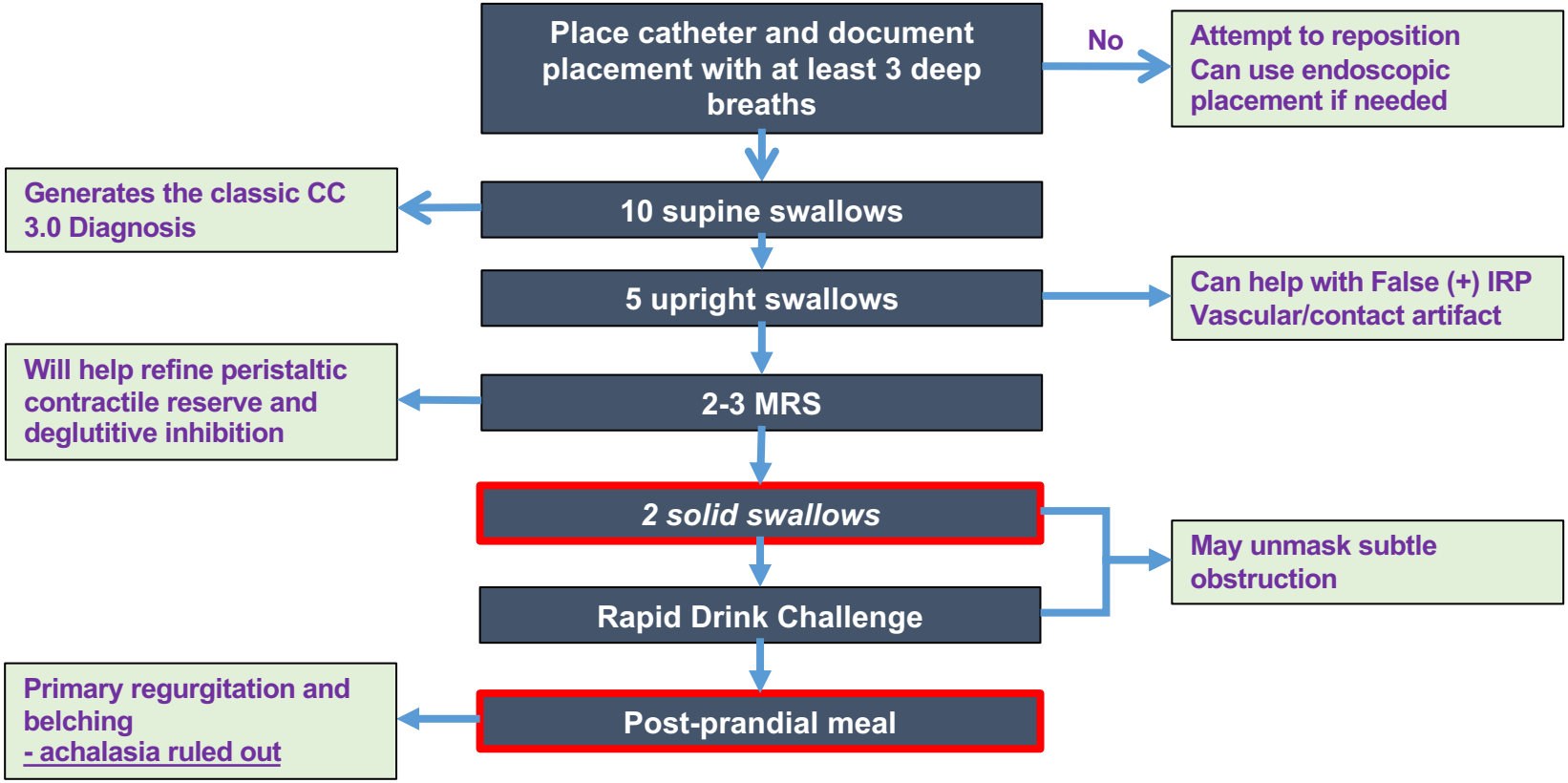
The Chicago Classification:4.0

Key updates in CCv.4.0 revolve around:

1. A more rigorous and expansive protocol that incorporates different positions and provocative testing.
2. A refined definition of esophago-gastric junction (EGJ) outflow obstruction (EGJOO).
3. An increased threshold for the diagnosis of ineffective esophageal motility.
4. An inclusion of a description of baseline EGJ metrics.
5. Further, the CCv4.0 sought to define motility disorder diagnoses as conclusive and inconclusive based on associated symptoms, the use of provocative testing and corroborating supportive testing with barium esophagram with tablet and/or functional lumen imaging probe.


Disorders of EGJ Outflow
Step 1: Perform 10 wet swallows (Primary position)
Abnormal median IRP
Yes
No
Step 2: Wet swallows in secondary position +MRS/RDC
Achalasia I
Yes
100% Failed Peristalsis without PEP
Achalasia II
Yes
100% Failed Peristalsis with PEP in ≥20% swallows
Yes
100% Absent Peristalsis All swallows are either failed or premature◊
Yes
Elevated LES IRP in varying positions ± elevated IBP/PEP
No
Achalasia III
Yes
≥20% swallows with premature contractions. Failed peristalsis ± PEP may be present
No
100% Failed Peristalsis
Yes
Absent Contractility
No
Step 2: (if not done) Wet swallows in secondary position + MRS/RDC
≥20% swallows with premature contractions
Yes
Distal Esophageal Spasm*
No
≥20% swallows with hypercontractility
Yes
Hypercontractile Esophagus*
No
Elevated LES IRP persists in varying positions + elevated IBP/PEP‡
No
No evidence of EGJ outflow obstruction
>70% ineffective or ≥50% failed swallows
Yes
Ineffective Esophageal Motility
No
Yes
EGJOO*†
Yes
Abnormal TBE or FLIP
No
No evidence of disorder of peristalsis
Consider meal challenges based on symptom¥
Disorders of Peristalsis

Chicago Classification 4.0 Protocol



The Chicago Classification:4.0

Key updates in CCv.4.0 revolve around:

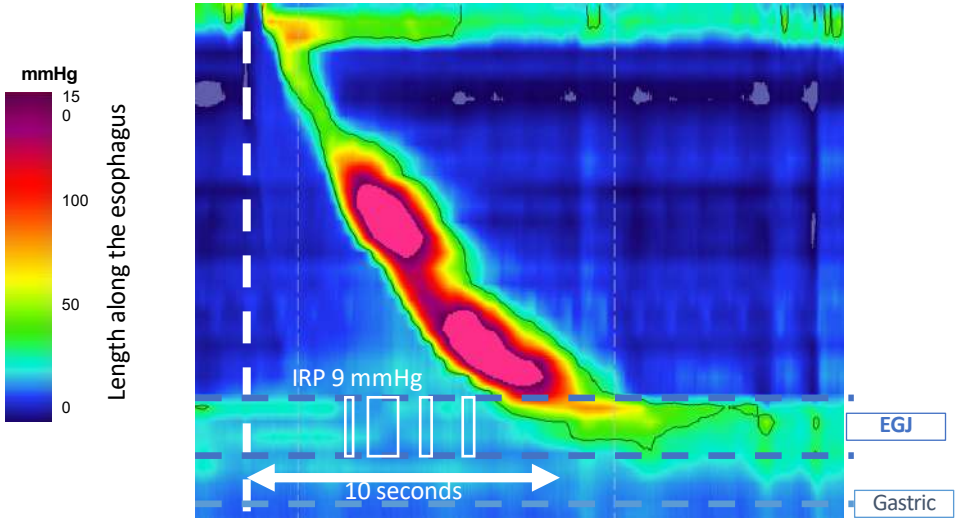
- Further, the CCv4.0 sought to define motility disorder diagnoses as conclusive and inconclusive based on associated symptoms, the use of provocative testing and corroborating supportive testing with barium esophagram with tablet and/or functional lumen imaging probe.

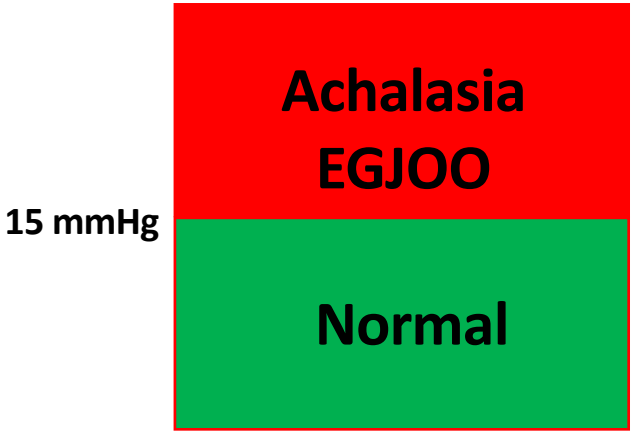
- *These changes attempt to minimize ambiguity in prior iterations.*
  - *Mostly related to issues around IRP*
  - *Also related to motor patterns seen in GERD that may be related to subtle obstruction or a small hernia.*

Integrated relaxation pressure (IRP)

The biggest problem with the Chicago Classification

- **Measures IBP driving the EGJ open [when it is open] or the LESP [when it is closed].**
- **Mean of the 4 seconds (contiguous or non-contiguous) of maximal deglutitive relaxation in the 10s following UES relaxation; referenced to gastric pressure**

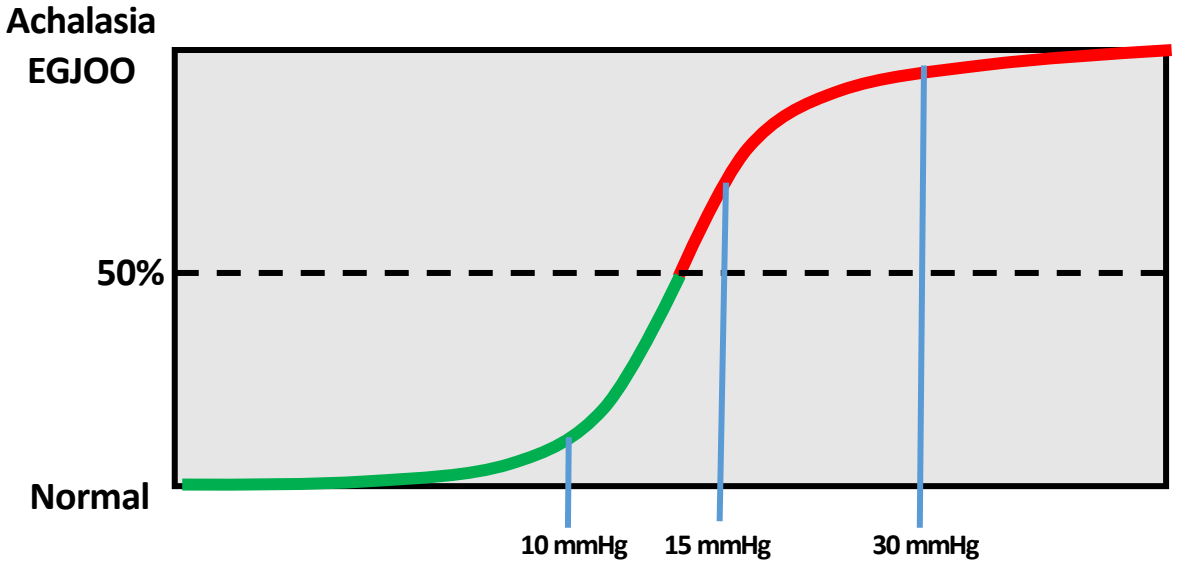




Integrated relaxation pressure (IRP)

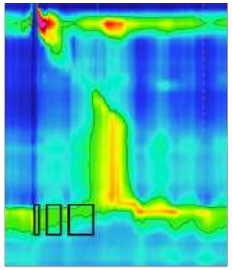
The biggest problem with the Chicago Classification

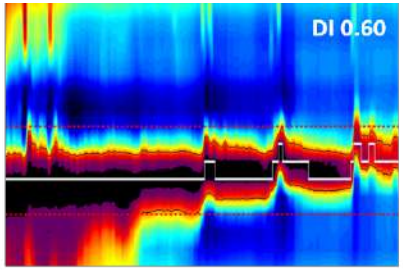
- **Measures IBP driving the EGJ open [when it is open] or the LESP [when it is closed].**
- **Mean of the 4 seconds (contiguous or non-contiguous) of maximal deglutitive relaxation in the 10s following UES relaxation; referenced to gastric pressure**



FUNCTIONAL LUMINAL IMAGING PROBE PANOMETRY: A METHOD TO DISTINGUISH TRUE EGJOO

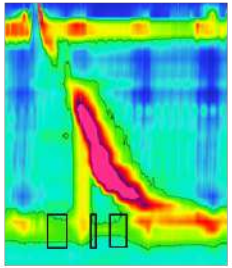
A. IRP 27.5 mmHg
DL 5.7 sec

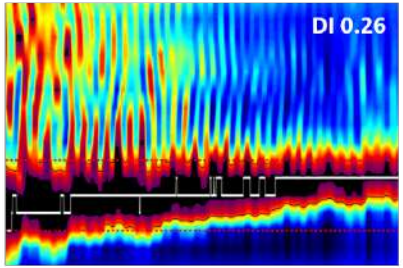




RAD-EGJOO:
Dilated Esophagus with
Liquid Barium Retention

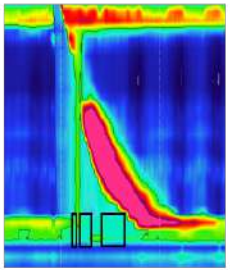
B. IRP 20.7 mmHg
DL 6.8 sec

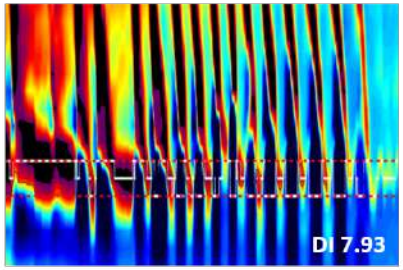




No RAD-EGJOO:
Abnormal Contractility
(Spasm/Tertiary Contractions)

C. IRP 24.4 mmHg
DL 5.1 sec





No RAD-EGJOO:
Liquid and Tablet Clearance
No abnormal Contractility

Summary

The Chicago Classification is not perfect.

- Achalasia classification good and there are some subtle issues
- EGJOO should never be diagnosed with manometry alone as most are normal.
- Jackhammer is a heterogeneous disorder and should be further phenotyped as most are not a primary motor abnormality.
- Weak peristalsis is a borderline motor disorder- but should not be forgotten.
- There are other patterns of motility occurring between and after swallows that may be important.
- So what is next?

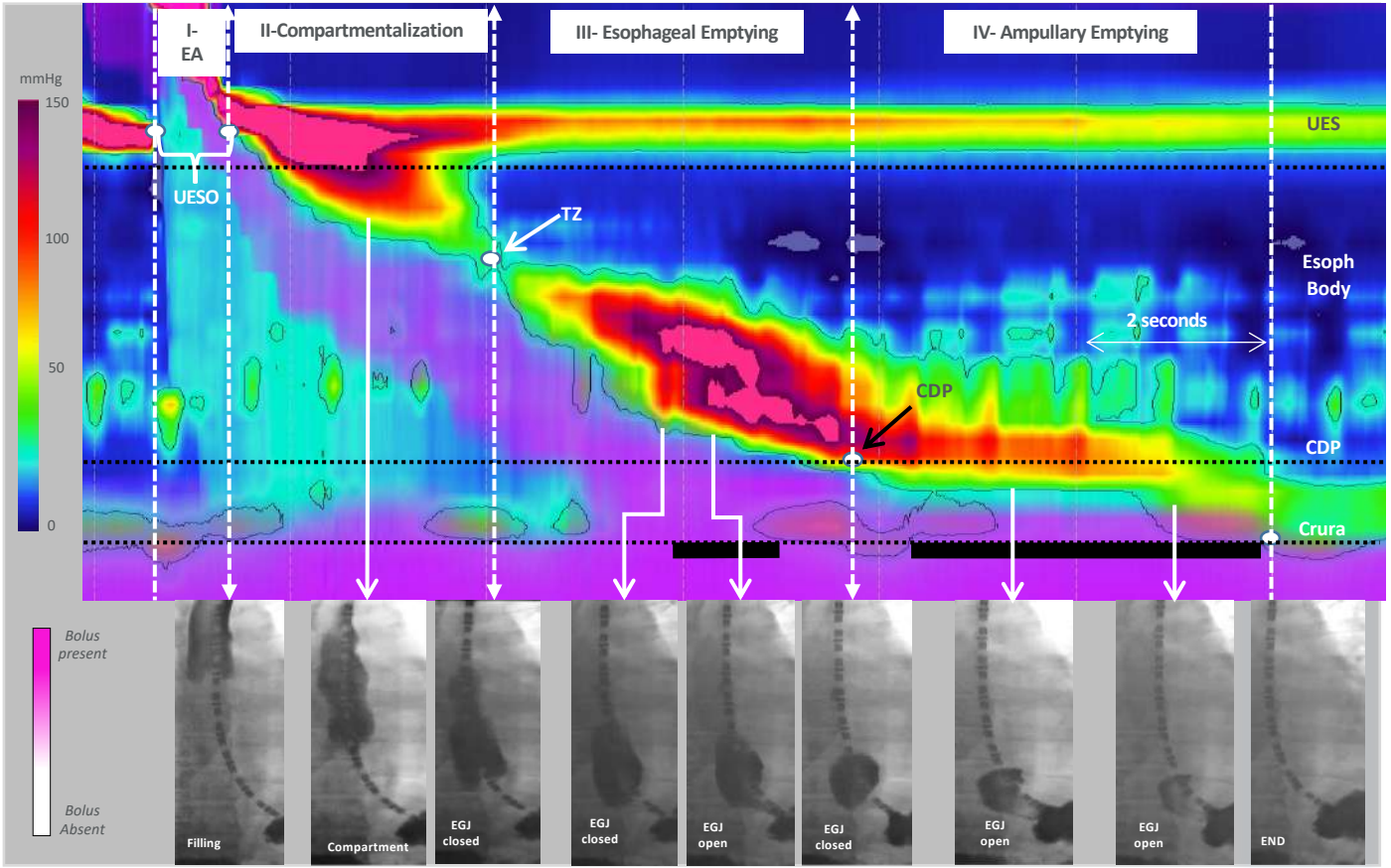
What is next?

- Chicago Classification 5.0 ?
  - Bringing in impedance to study the interplay between bolus transport and motor function.
  - Better assess geometry and mechanics of bolus transport.

- FLIP-Panometry
  - Assessing the response to volumetric distention- secondary peristalsis
  - Understanding EGJ Opening dynamics beyond LES relaxation

The 4 phases of Esophageal Bolus Transit

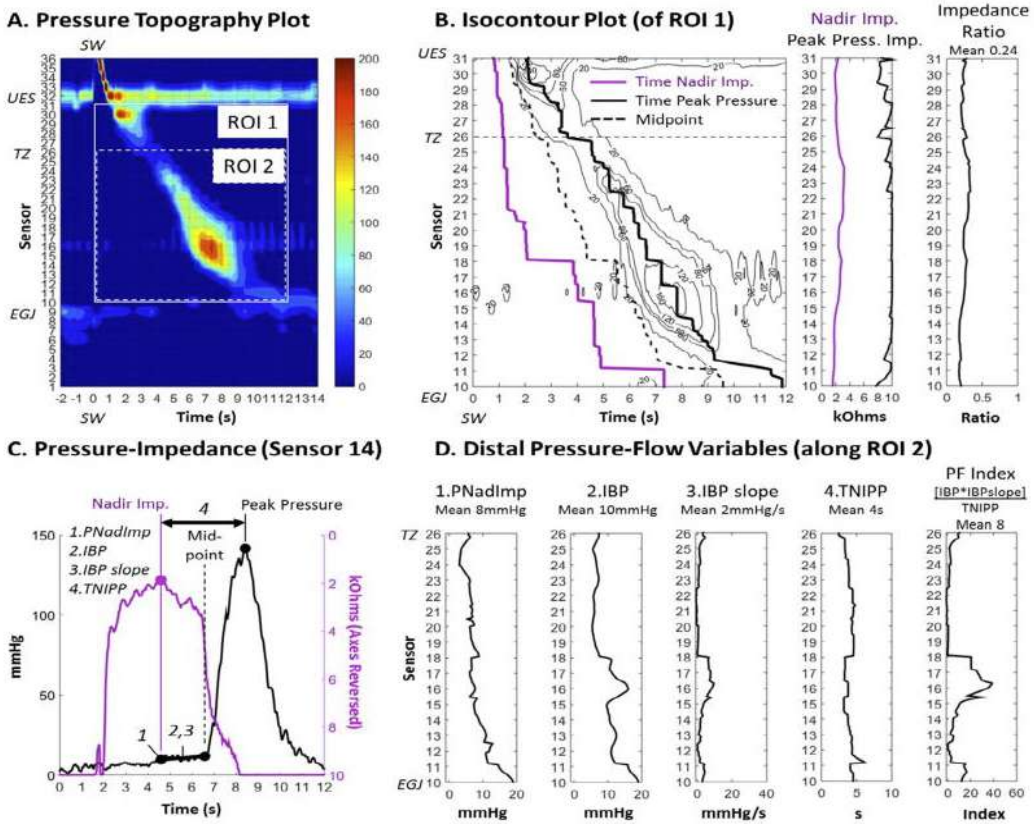
Redefining Esophageal Function

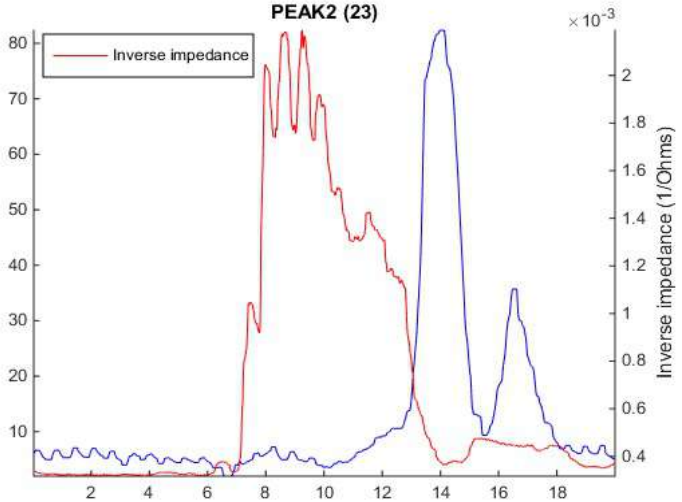


Lin, Z. Am J Physiol Gastrointest Liver Physiol. 2014 Aug 15;307(4):G437-44.

Quantifying Bolus retention beyond HRIM

Assessing geometry-pressure changes using impedance

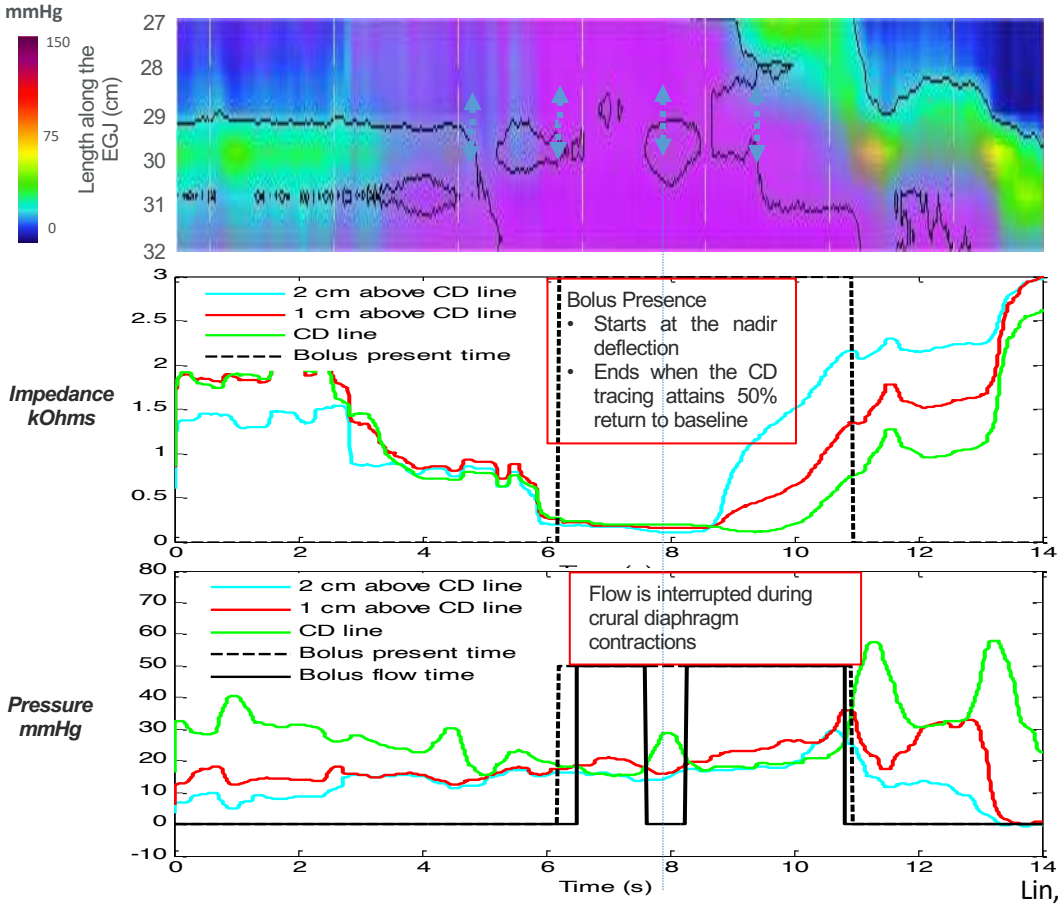




Carlson et al. Neurogastroenterol Motil. 2017 Mar ; 20 (3).

Using HRIM-to improve the IRP and define retention

Defining Flow Time and EII using the HRIM Sleeve

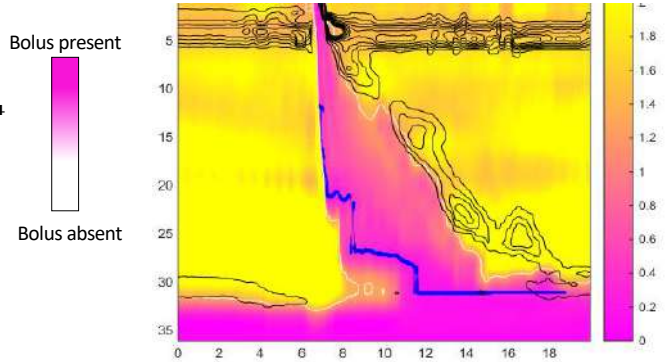


Comparison of maximal esophageal diameter and concurrent mean pressures at the landmark measurement times. Distensibility, approximated by diameter/pressure, was greatest during phase II

	Pressure, mmHg	Diameter, mm	Diameter/Pressure, mm/mmHg
End of Phase I	10.0(6.7–14.5)	19.8 (15.0–25.0)	2.1 (1.3–3.0)
End of Phase II	8.9 (6.4–12.1)	28.3 (23.5–30)*	3.5 (2.2–4.2)*†
End of phase III	12.9 (11.0–15.4)	27.5 (25.0–30.4)*	2.1 (1.7–2.4)

*$P < 0.05$ vs. upper esophageal sphincter;
†$P < 0.05$ vs. contractile deceleration point (CDP).

Esophageal Impedance Integral

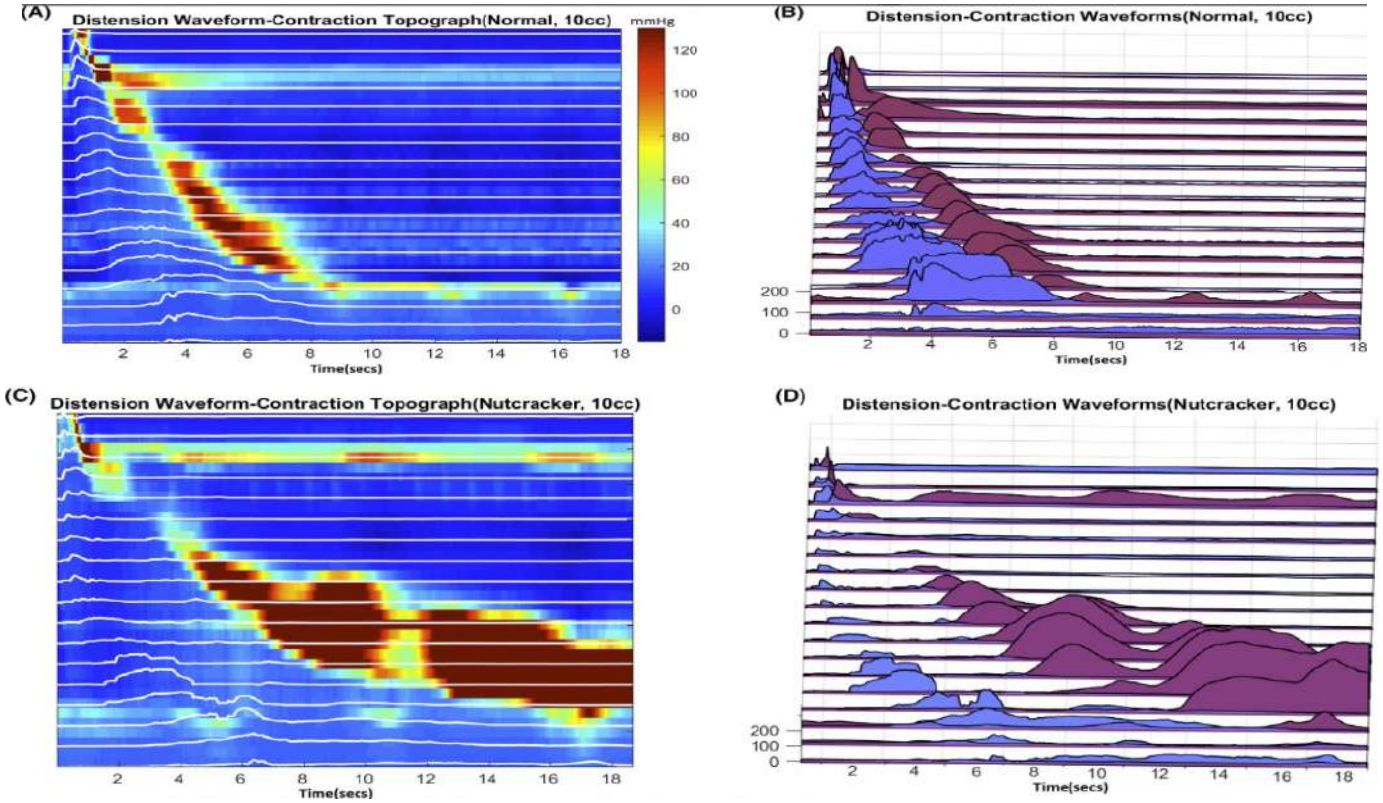


Lin, Z. Neurogastroenterol Motil. 2015 Sep;27(9):1232-8.

Lin, Z. Am J Physiol Gastrointest Liver Physiol. 2014 Aug 15;307(4):G437-44.

Quantifying Bolus Transit beyond HRIM

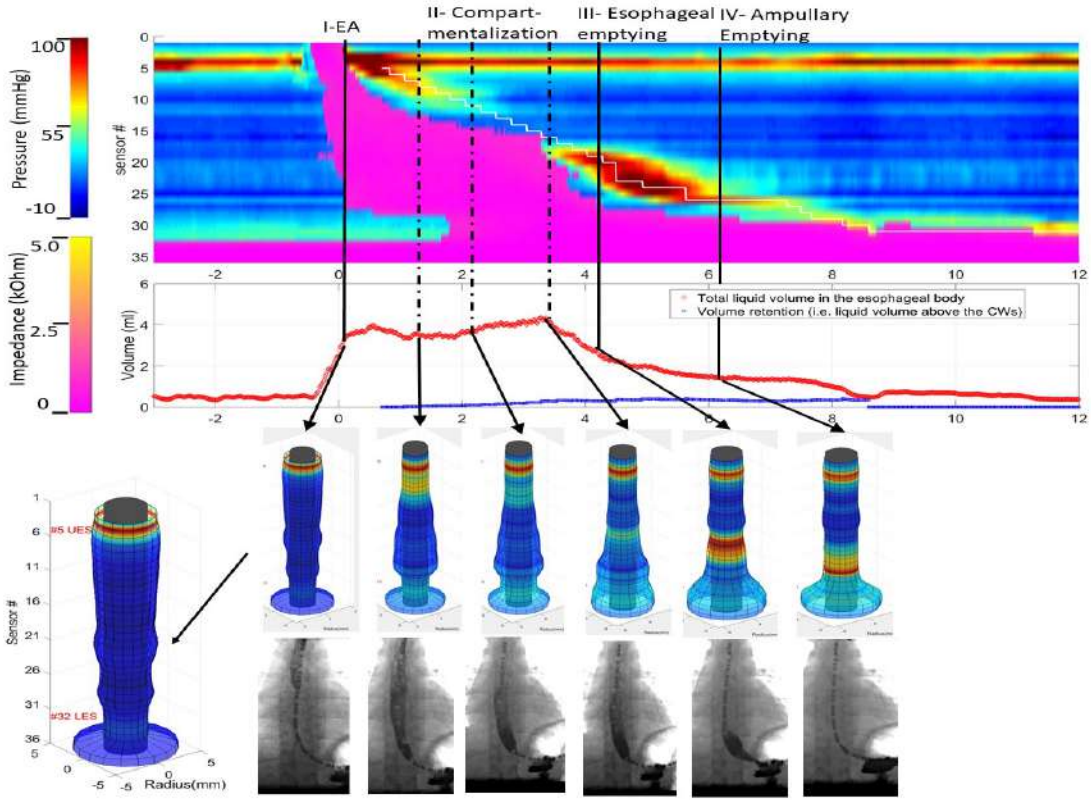
Distention Plots

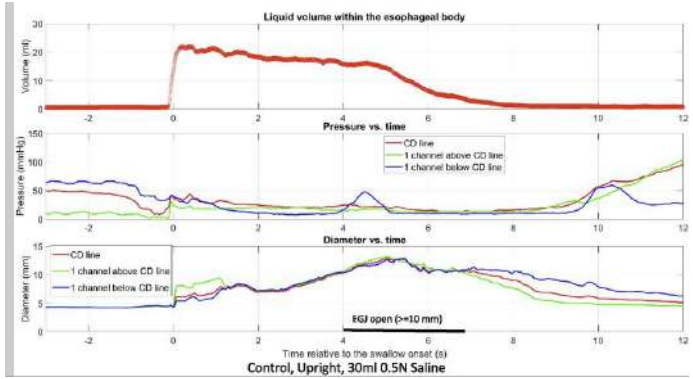


Zifan et al. Neurogastroenterol Motil. 2021 Apr 5;e14138..

Quantifying Bolus retention beyond HRIM

Assessing geometry-pressure changes using impedance





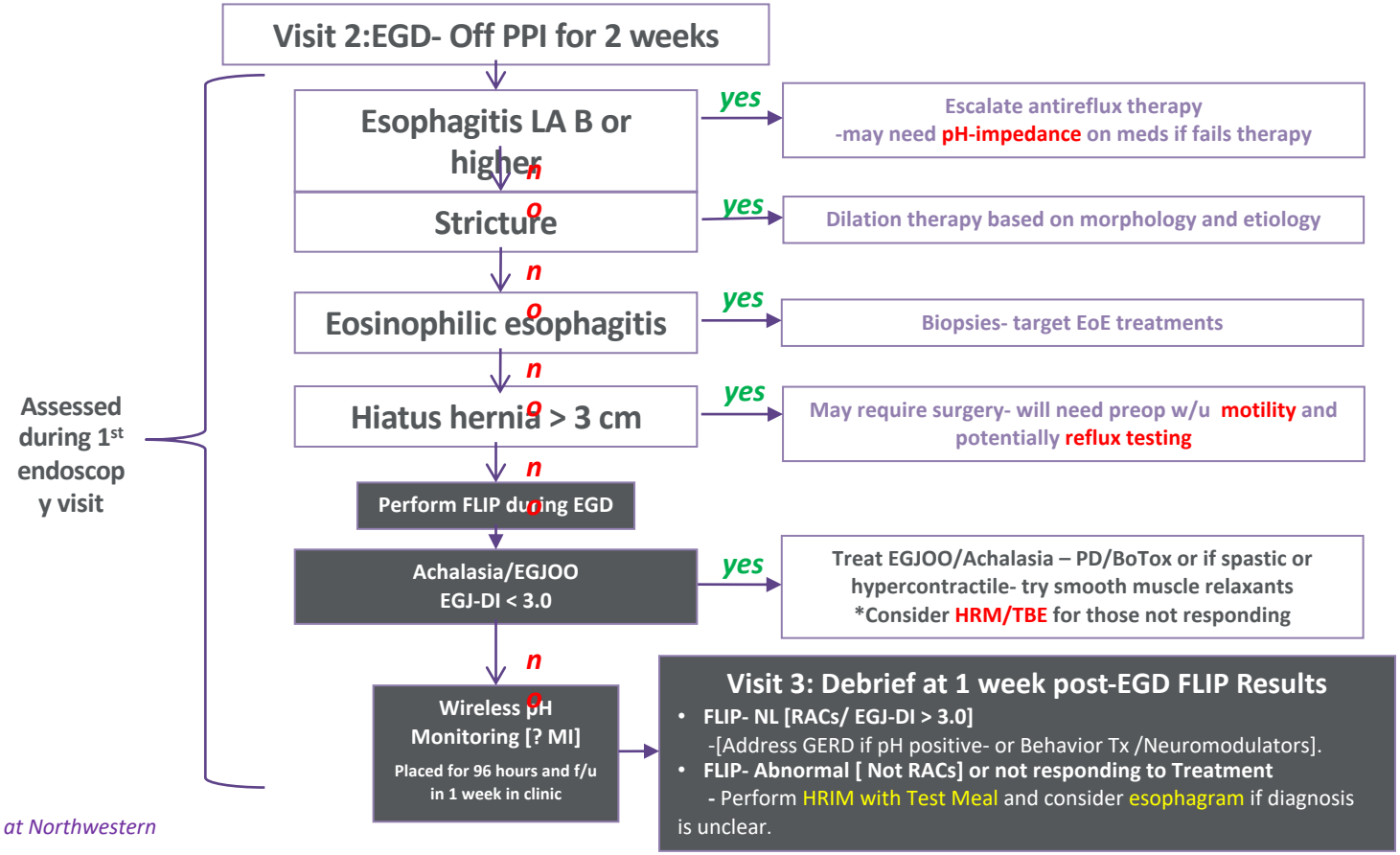
New metrics with 4D manometry

- *Volume retention*
- *Patterns of emptying*
- *More accurate measure of IBP*
- *Length-tension curves and wall stiffness*
- *EGJ-DI and EGJ cross-sectional area*
- *Esophageal work and Power*

Kou et al. Therap Adv Gastroenterol. 2020 Oct 24;13:1756284820969050 .c

Approach to patient with esophageal complaints:

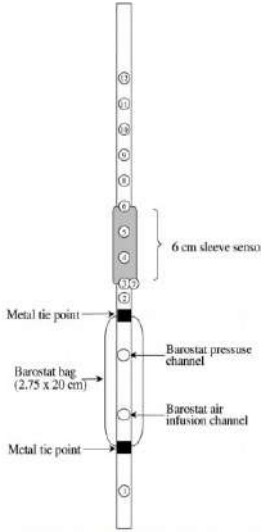
Visit 1: Dysphagia, Chest Pain, Food Impaction, Regurgitation not responding to PPI

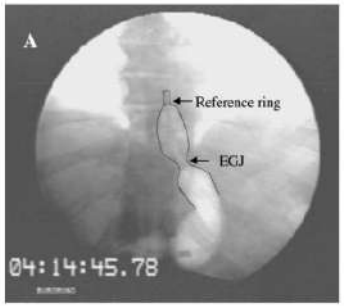


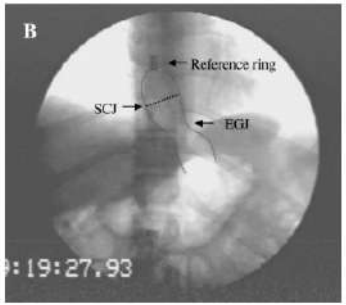
Response to Volumetric Distention- Distensibility

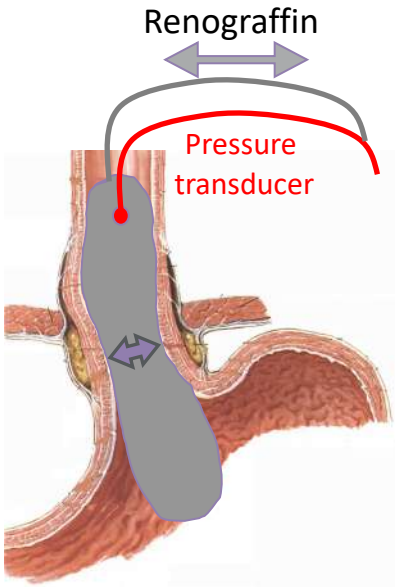
- Measuring Mechanical Properties of the Esophagus

Barostat → Hydrostat → Functional Lumen Imaging Probe

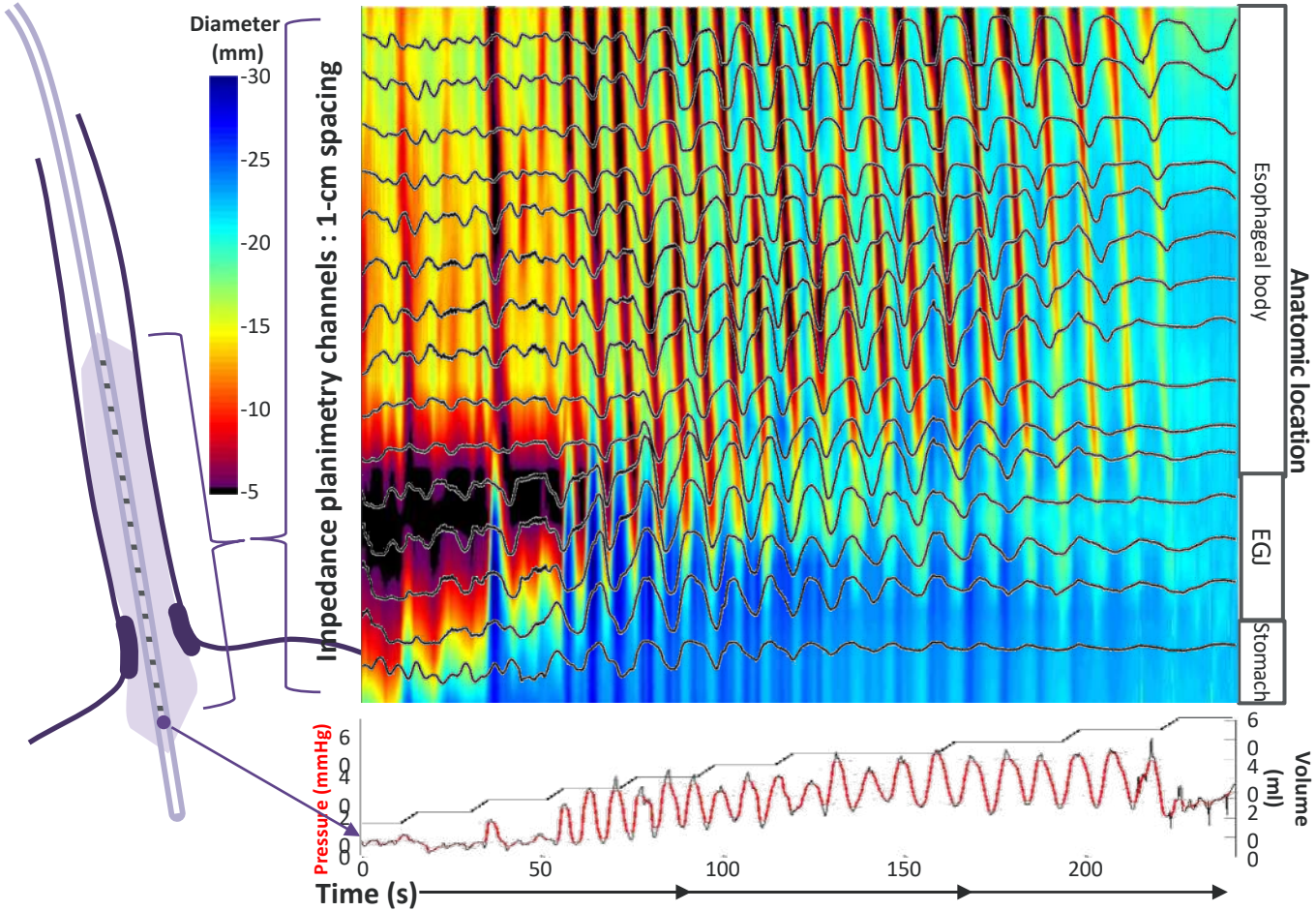




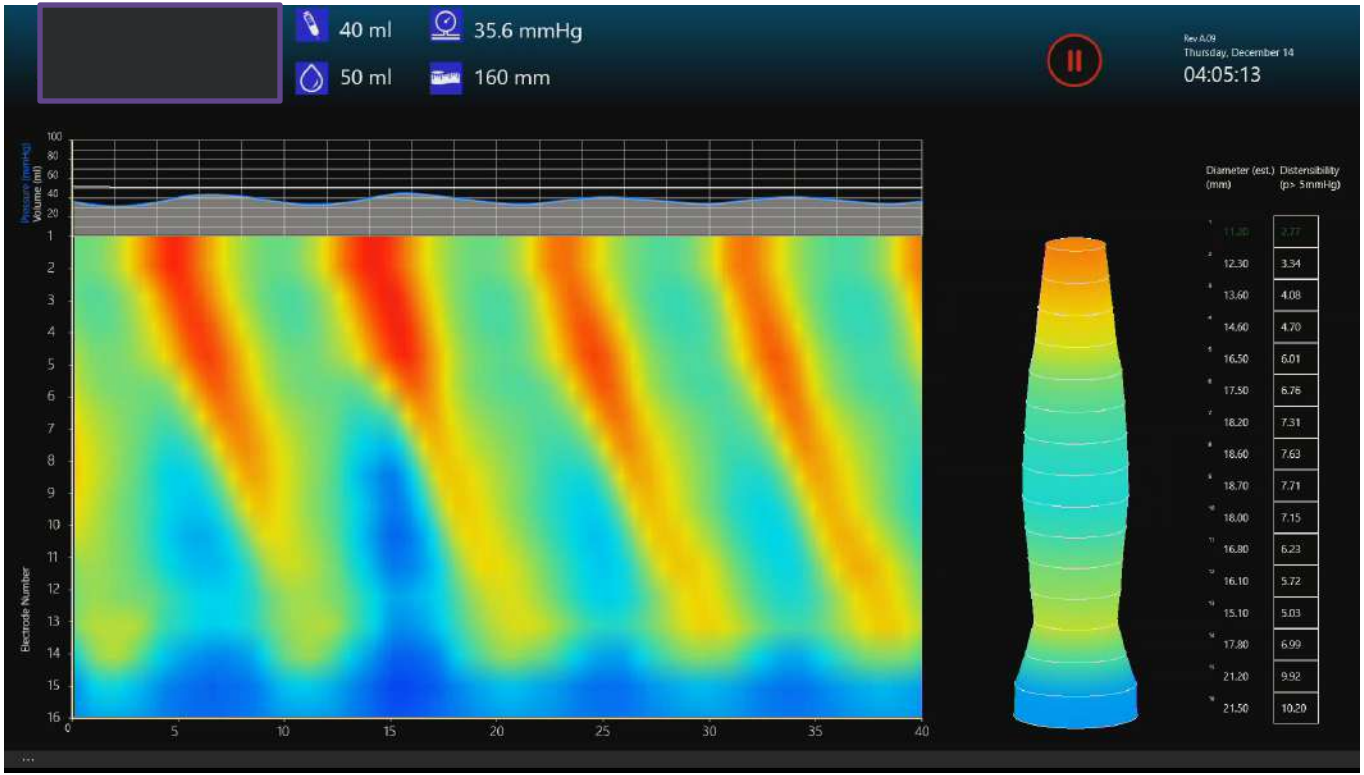




Flip Panometry: Esophageal *diameter* topography



Flip Panometry: Assessing Esophageal Function using Topography

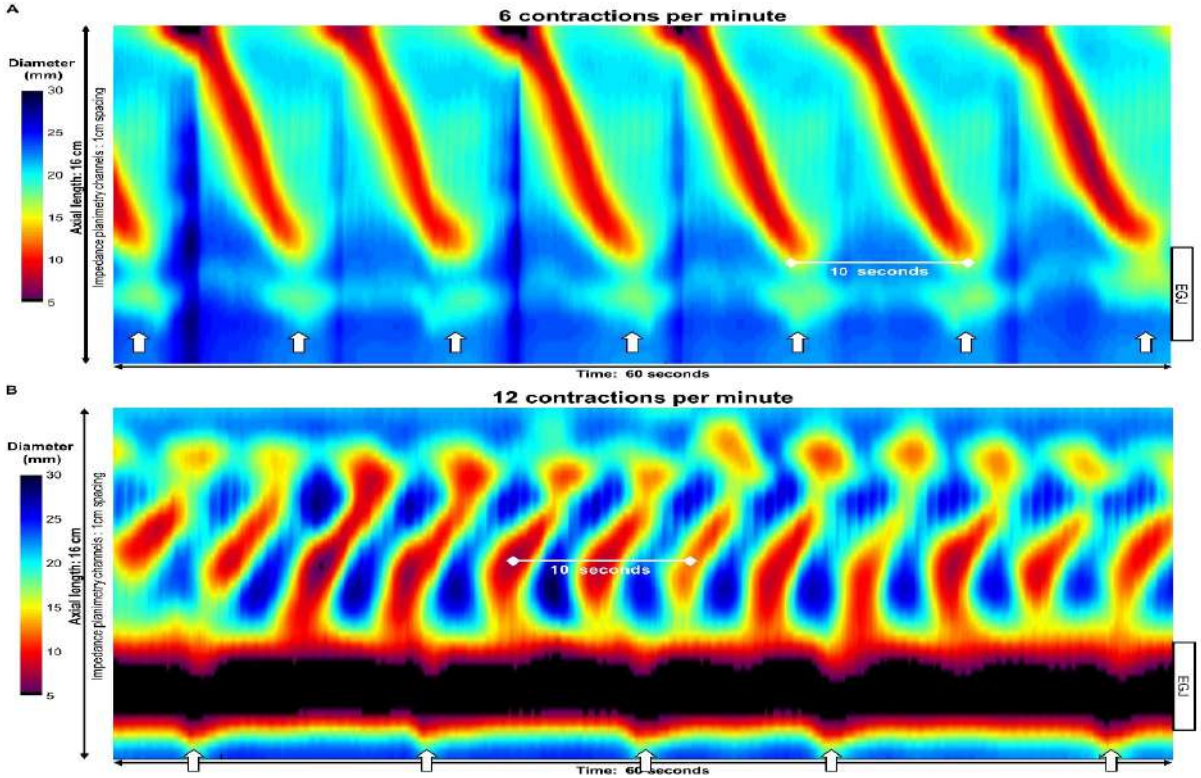


Esophageal Symptoms
What FLIP Panometry can do during the index EGD

- Assess peristalsis by triggering secondary peristalsis.
  - Can separate motility into physiologic and clinically relevant patterns to assess peristaltic function [Swallow type, DCI on HRM]
- Assess EGJ Opening dynamics.
  - IRP on HRM, EGJ opening on TBE
- Provide an estimate of esophageal stiffness and determine the minimal diameter for impaction risk for EoE patients and strictures.
  - Determine minimal diameter similar to esophagram and compliance of the esophagus
- Potentially guide esophageal surgery.
  - Intraoperative and post-operative evaluation

Rate of RACS: *Rule of 6*

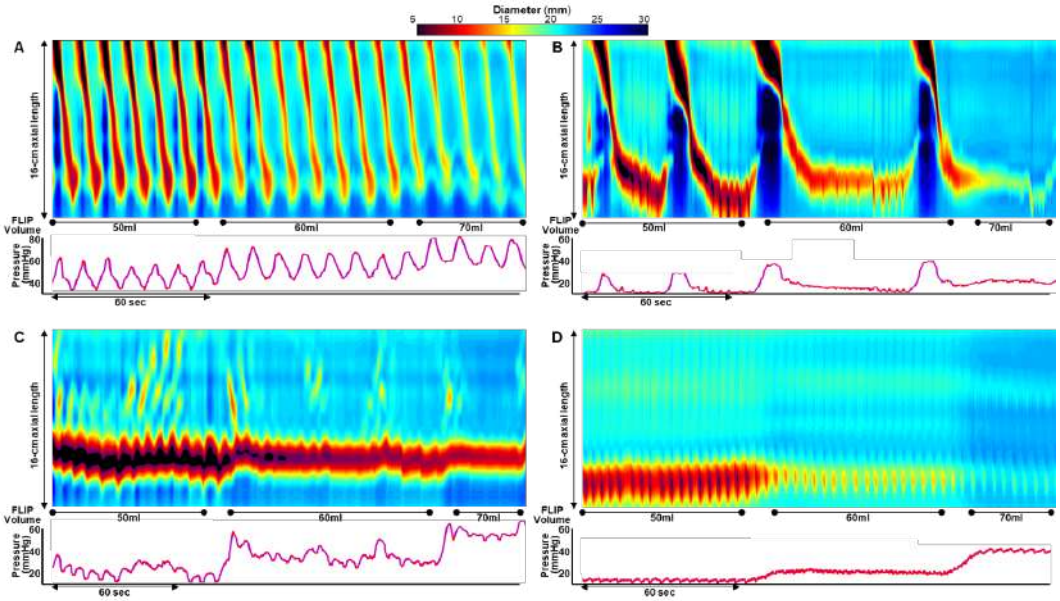
- At least 6 repeating lumen occlusions longer than 6 cm at a consistent rate of 6 (+/- 3) per minute
- Governed by the the inhibitory gradient and refractory period of the esophagus
- ?Pacemaker

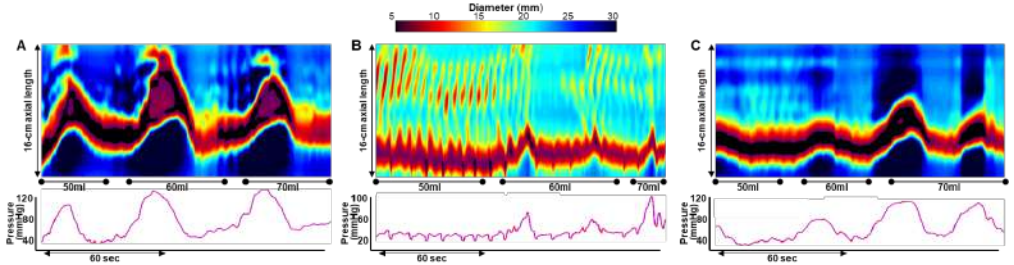


FLIP Panometry

Contractile patterns

Panometry Contractile Response Patterns	Definition
Normal Contractile Response NCR	RAC-Rule of 6s (Ro6s) • ≥6 consecutive AC's of • ≥6 cm in axial length occurring at • 6+/-3 AC per minute regular rate
Borderline Contractile Response BCR	• Not meeting RAC Ro6 • Distinct AC of at least 6-cm axial length present • May have RCs - but not RRCs • No SOCs or sLESCs
Impaired/Disordered Contractile Response IDCR	• No distinct ACs • May have sporadic or chaotic contractions not meeting ACs • May have RCs- but not RRCs • No SOCs
Absent Contractile Response ACR	• No contractile activity in the esophageal body
Spastic-Reactive Contractile Response SRCR	• SOC or • sLESC or • RRCs- at least 6 RCs at rate > 9 RCs per minute • May have sporadic AC's



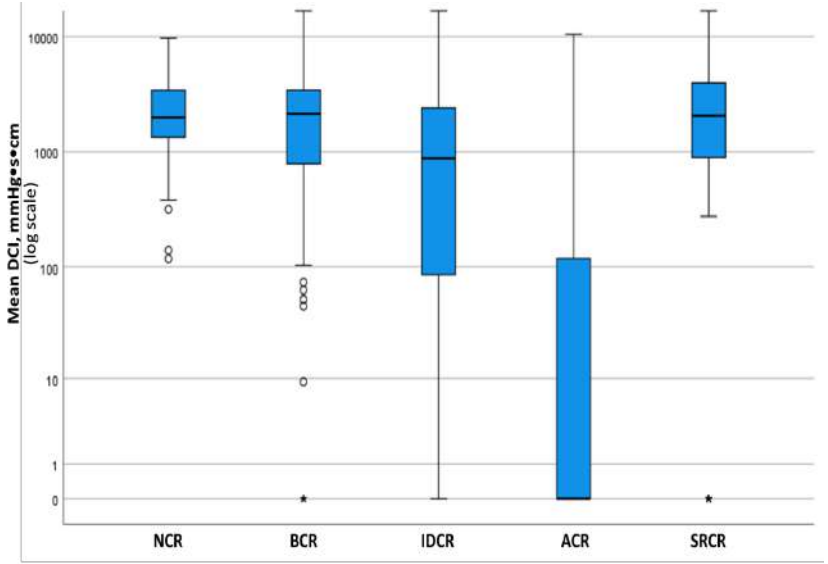


FLIP Panometry

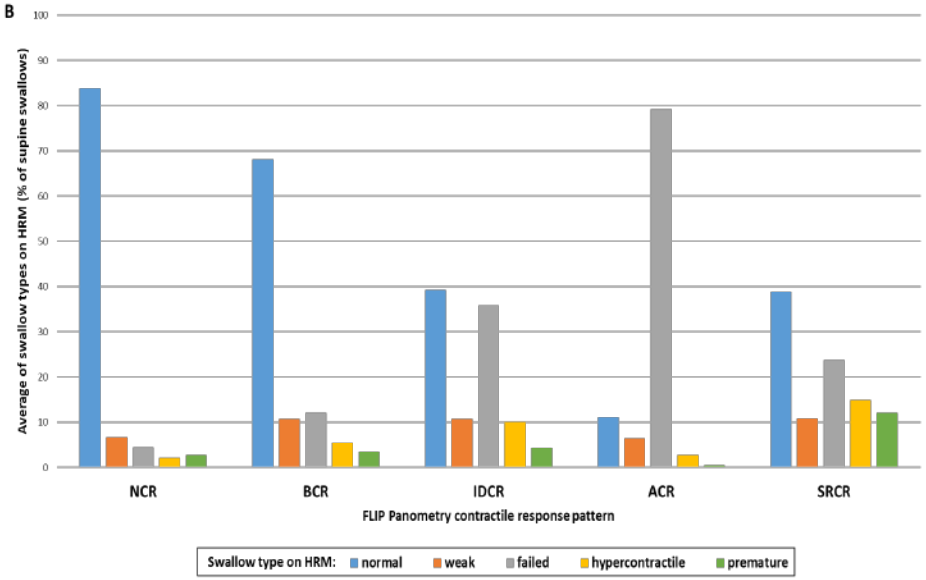
Contractile patterns in 706 patients with FLIP and HRM

Validation of contractile patterns using HRIM metrics.

Peristaltic vigor on high-resolution manometry (HRM) differed by FLIP Panometry contractile response pattern.

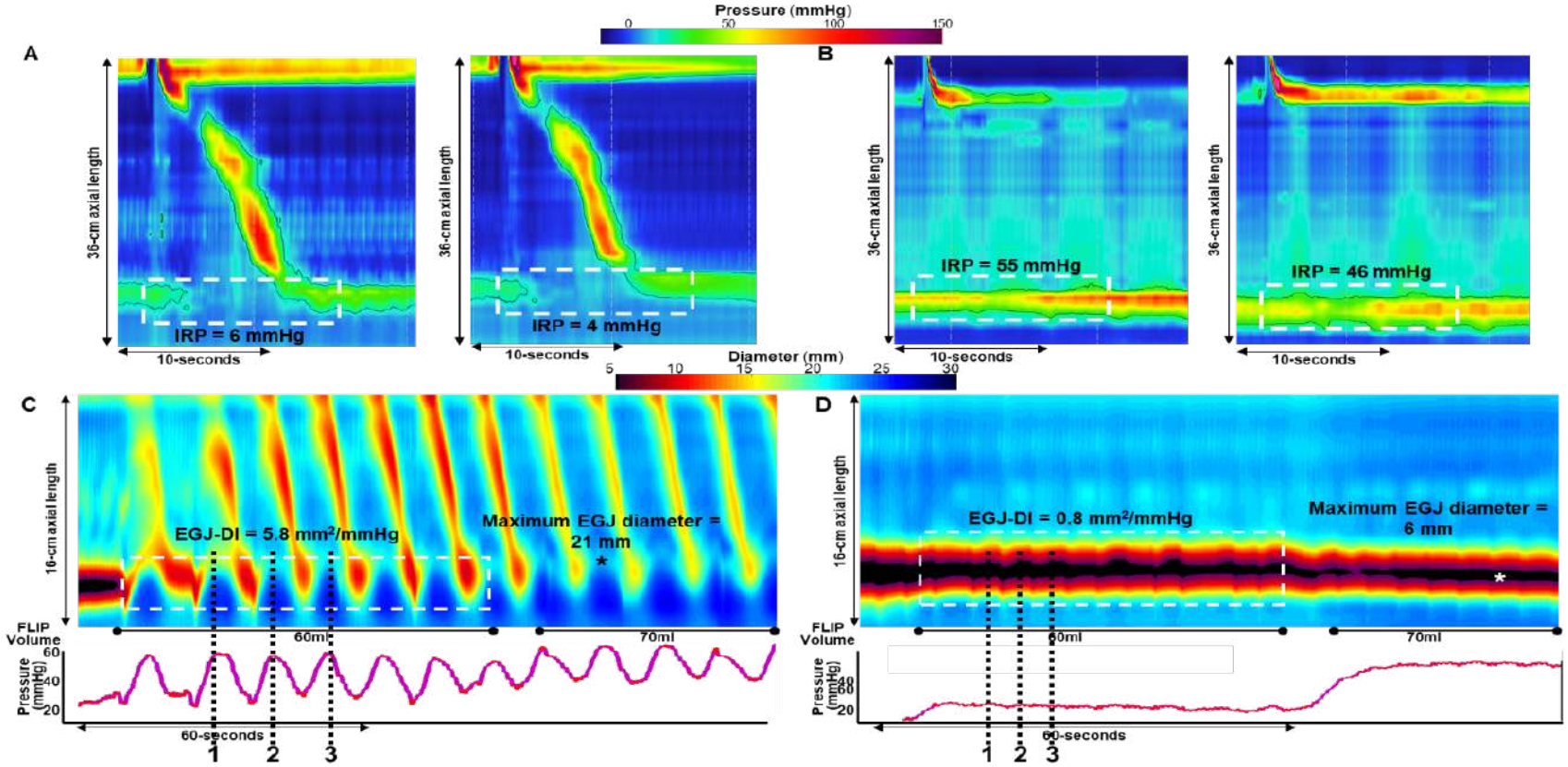


Swallow types on high-resolution manometry (HRM) differed by FLIP Panometry contractile response pattern.



Assessing EGJ Opening Dynamics in the context of peristalsis

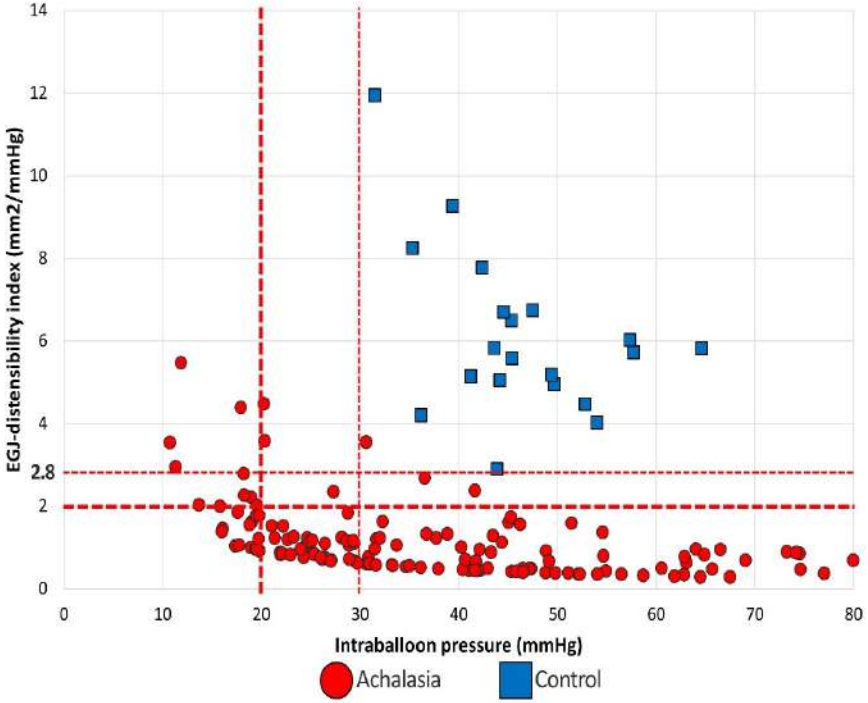
Balancing EGJ-DI and Max Diameter



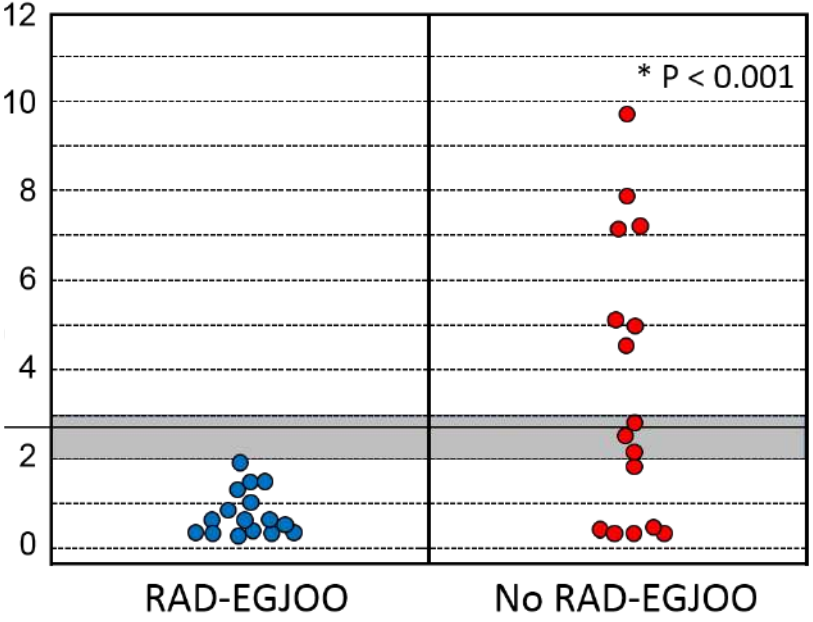
EGJ-distensibility index (EGJ-DI) in Achalasia and EGJOO

- **EGJ-DI =** Narrowest **CSA_{EGJ}** / intra-balloon **pressure**

DISTINGUISH ACHALASIA FROM NORMAL



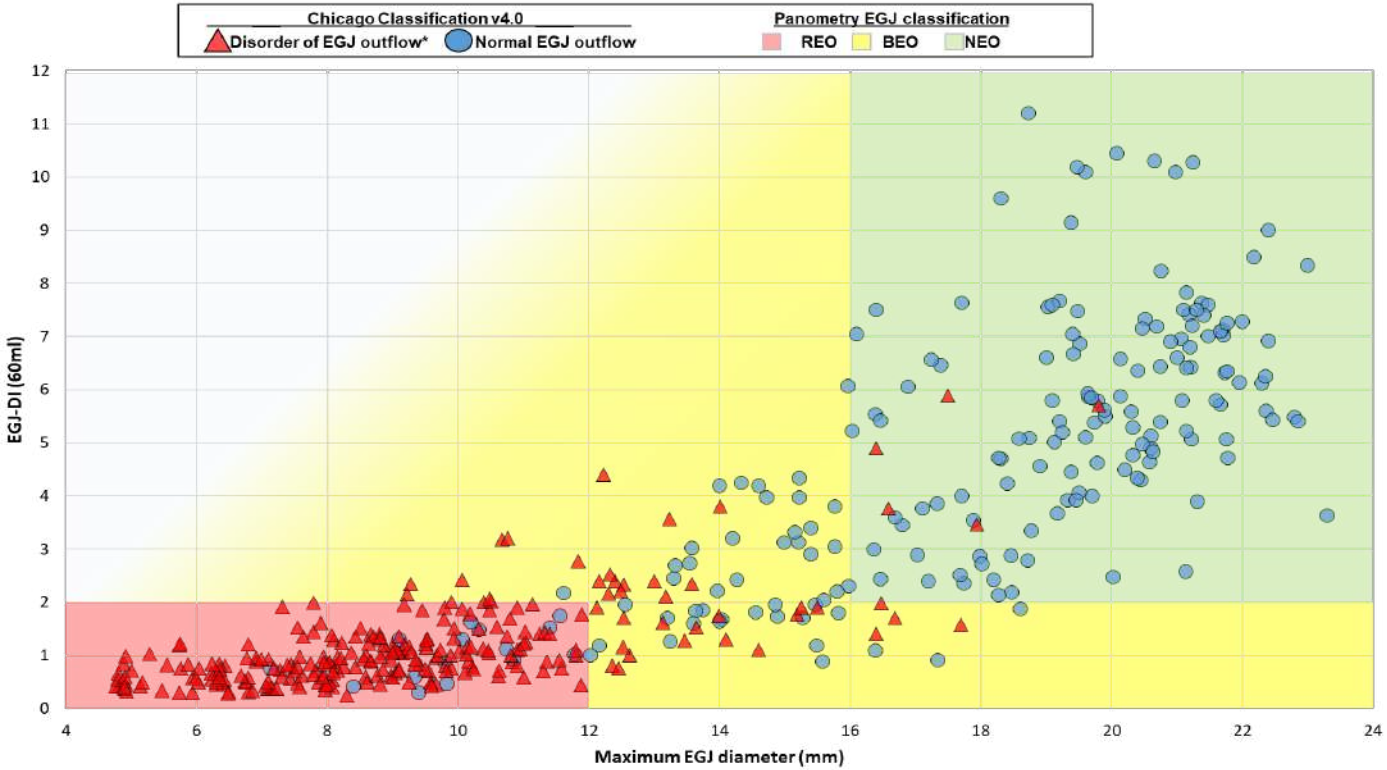
DISTINGUISH TRUE EGJOO



Assessing EGJ Opening Dynamics in the context of peristalsis

Balancing EGJ-DI and Max Diameter

Association of FLIP Panometry esophagogastric junction (EGJ) opening parameters with esophagogastric junction (EGJ) obstruction based on the Chicago Classification v4.0.

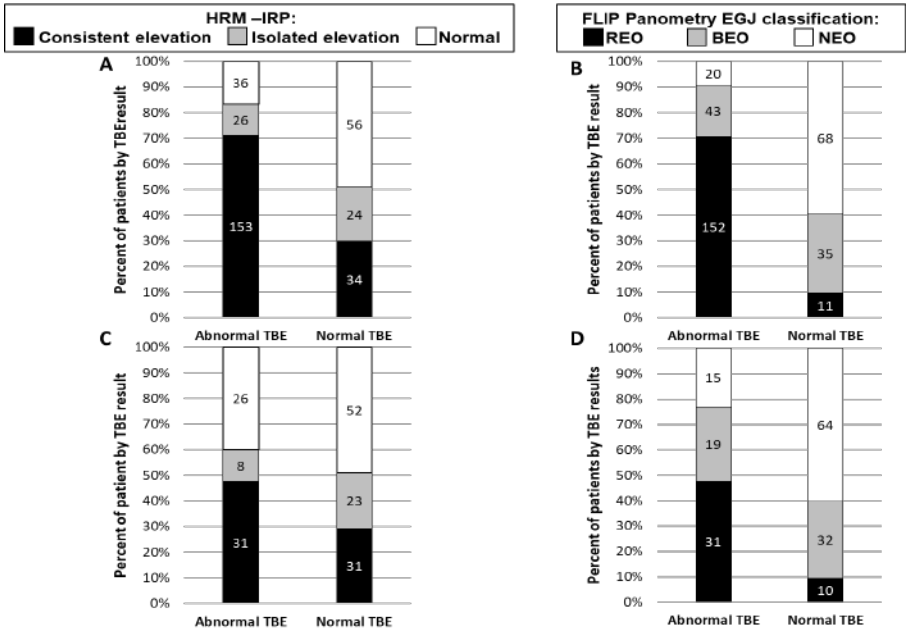


Assessing EGJ Opening Dynamics in the context of peristalsis

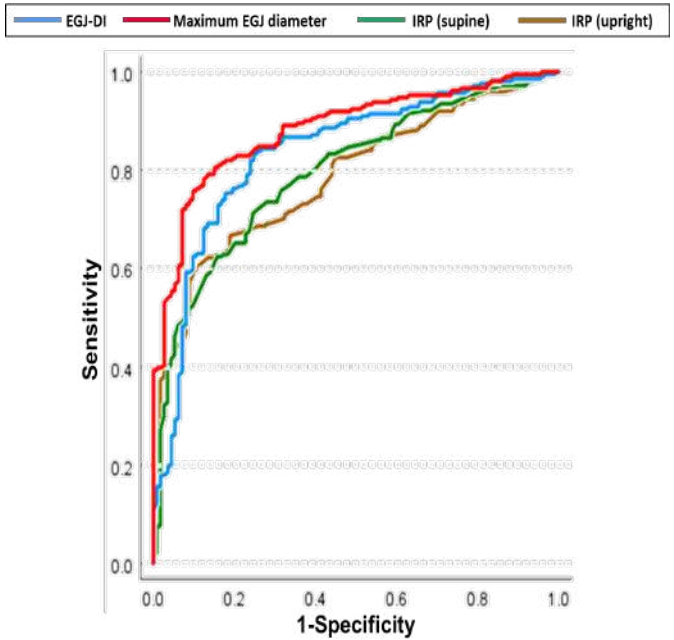
Balancing EGJ-DI and Max Diameter

Validation with Esophagram and Comparison to IRP

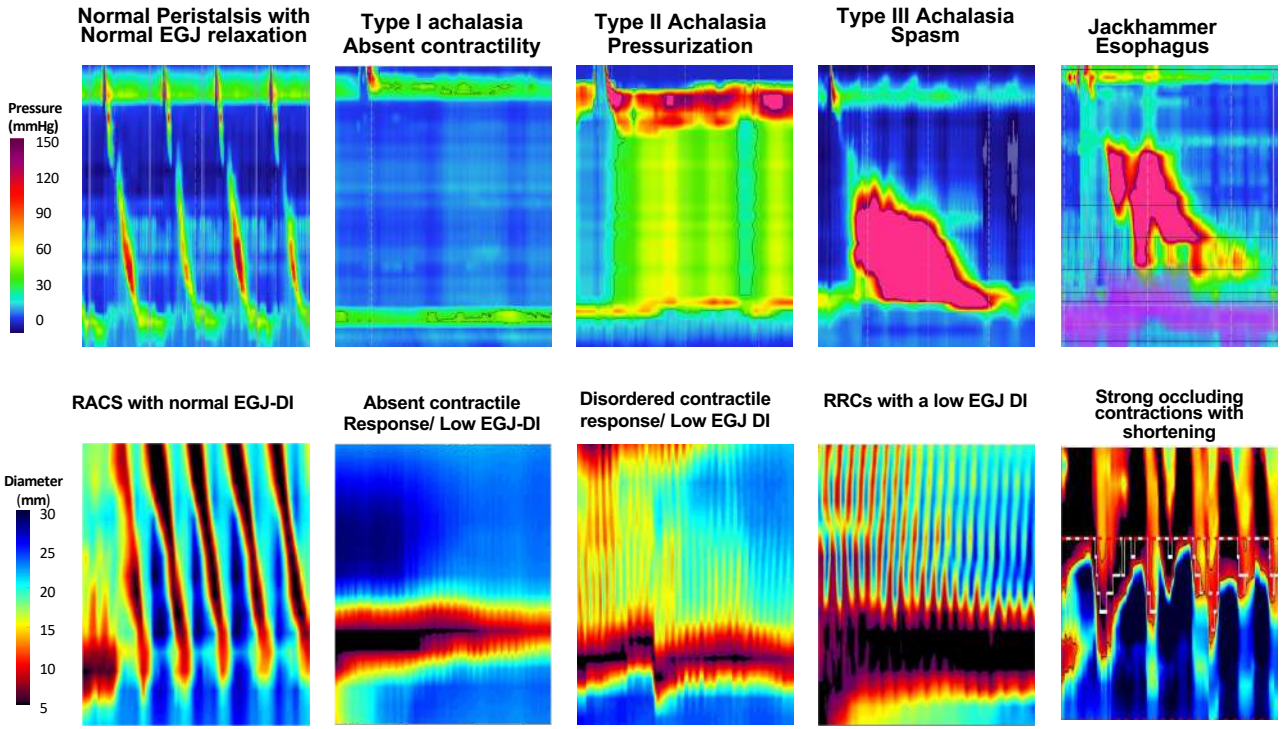
Association of high-resolution manometry (HRM; A and C) and FLIP Panometry (B and D) results with timed barium esophagram (TBE).



Receiver operating characteristic (ROC) curves for identification of abnormal esophagram.



FLIP Panometry: Contractile Patterns- Tempting to mimic CC



FLIP Panometry

How do we use Panometry in clinical practice

Perform EGD

- Mechanical Obstruction
- Inflammation
- Large Hiatus Hernia
- EoE

- EGD- Negative

Identify FLIP Pattern

- NCR
- BDCR
- IDCR
- ACR
- SRCR

Assess Obstruction

- NEO
- BEO
- REO
- Distensibility- Body/EGJ

Determine classification based on EGD, FLIP Pattern and EGJ Opening

Clinical Decision

Normal [NEO + NCR/BDCR]
- Rule out GERD
- Consider functional disorder [CBT/GDH]

Obtain Bravo and consider functional dx if Bravo (-)

Weak [NEO + ACR/IDCR]
- GERD
- Consider SSC or IEM

Obtain Bravo and consider HRM to support DX

Non-spastic obstruction [REO + ACR/IDCR]
- Achalasia- will not require tailored
- Reactive LES [Based on EGD/Assess emptying]

TBE and/or HRM for reactive LES or ? EGD correlation

Spastic [Evidence of SRCR]
- Achalasia III, Spastic Disorder or Jackhammer

Obtain HRM to rule out type III achalasia and assess for spastic disorder, hypercontractile disorder

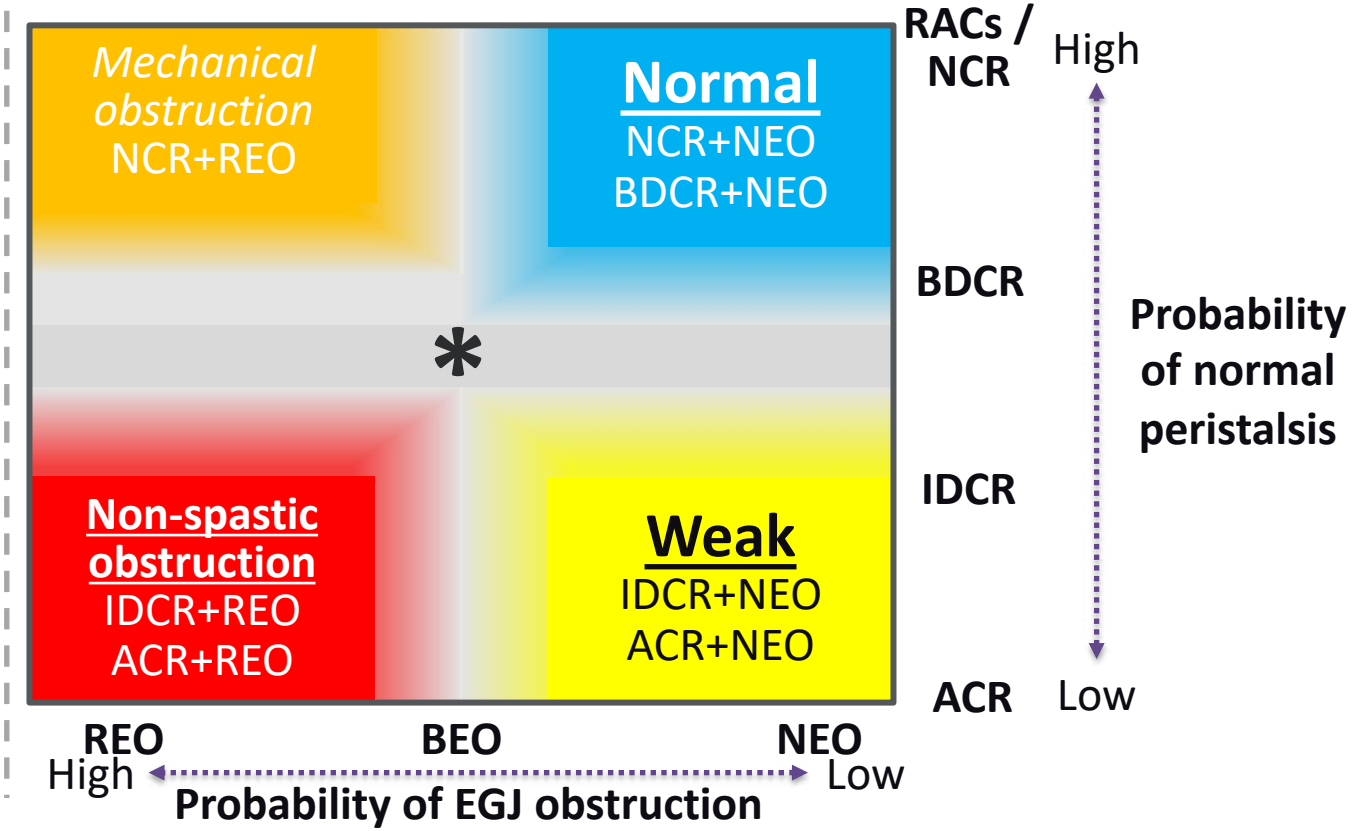
Indeterminate – Possible Mechanical EGJOO
[REO/BEO + NCR/BDCR or Abnormal DP]
Attempt targeted dilation and consider HRIM and/or esophagram if no response

Indeterminate – Possible Achalasia
[BEO + IDCR/ACR]
Attempt targeted dilation [BoTox?]and consider HRIM and/or esophagram if no response

FLIP Panometry:
Proposed classification of esophageal motility

SPASTIC-REACTIVE*
- SOCs
- RRCs
- sLESC

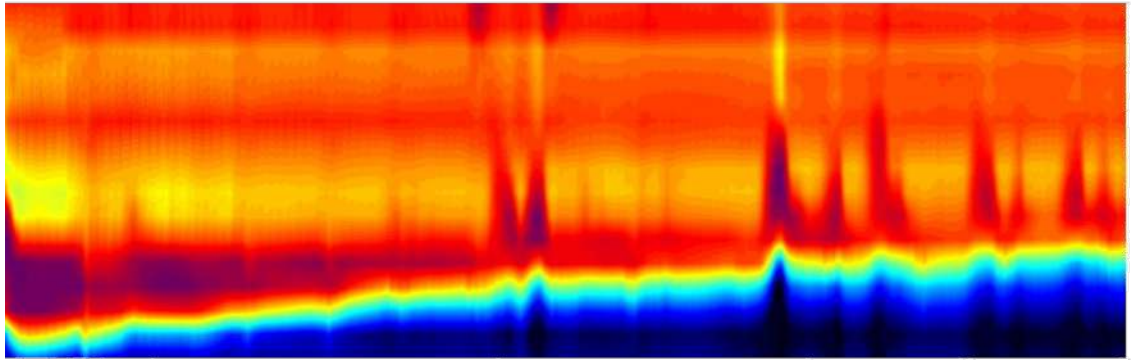
*Obtain HRIM +/- TBE to further assess motility and rule out achalasia.



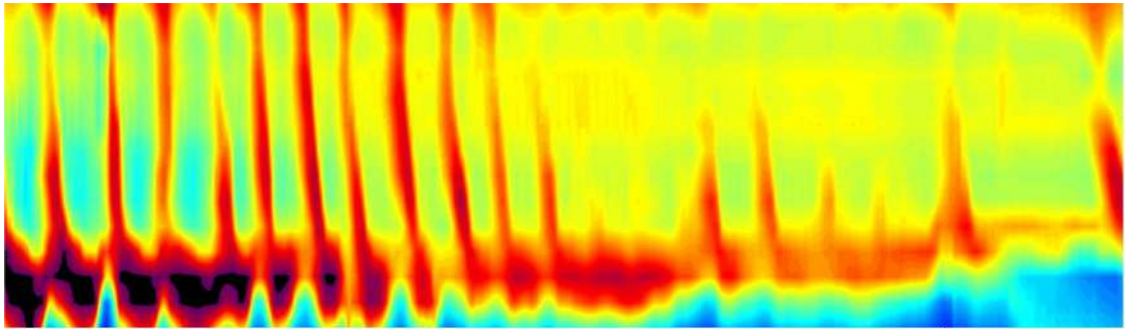
*Correlate/ complement w/ HRIM +/- TBE

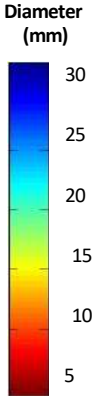
Changes in distensibility before and after Budesonide

Before Budesonide: No peristalsis, narrow and poorly distensible esophagus with a distensibility plateau of 7 mm (red)



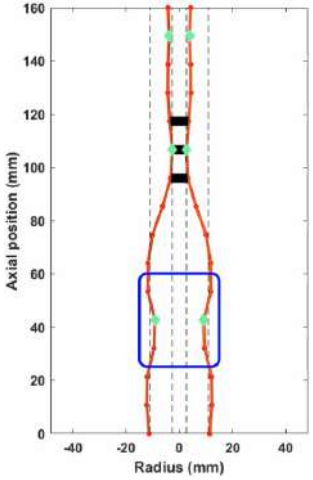
After Budesonide: Peristalsis returns and the esophagus is more distensible with a distensibility plateau of 13 mm (yellow)

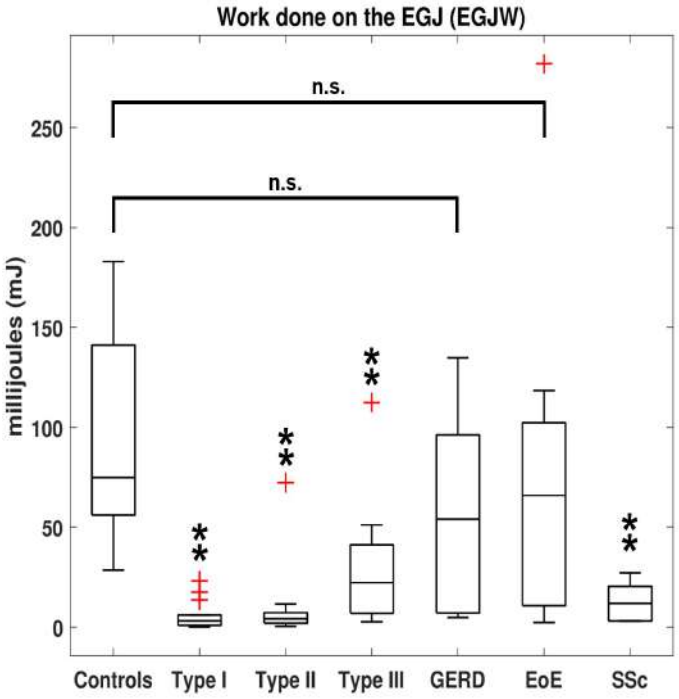


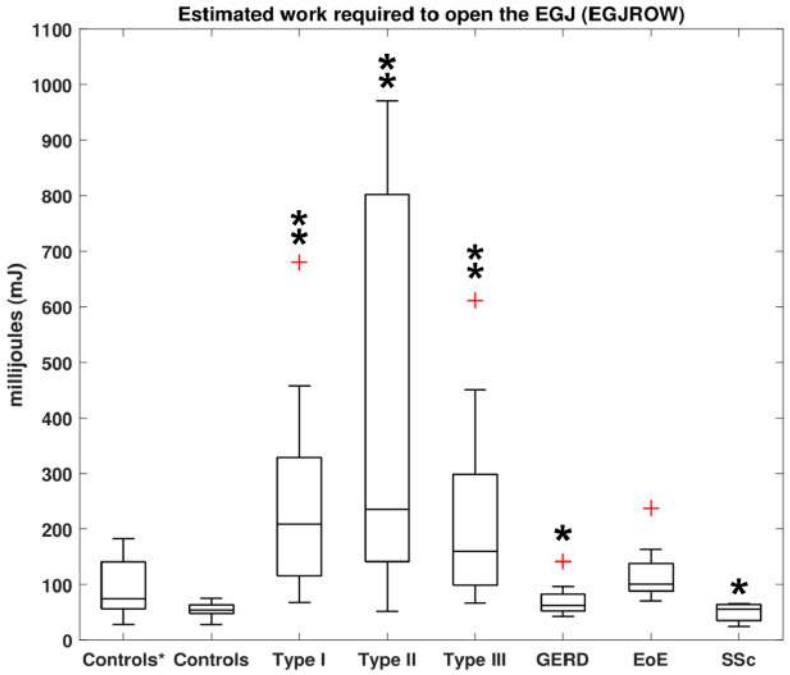


Carlson et al. Clin Transl Gastroenterol. 2017 Oct 5;8(10):e119

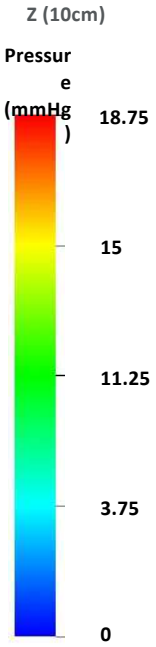
Variations of EGJ work done (EGJW) and work to open the EGJ (EGJOW) Across disease groups compared to controls.

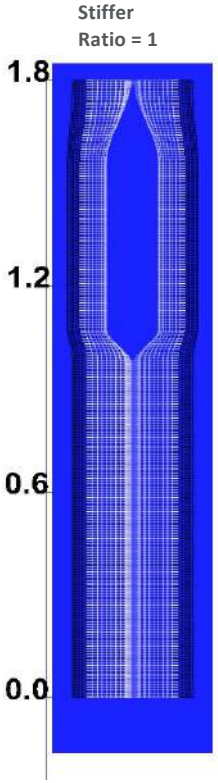


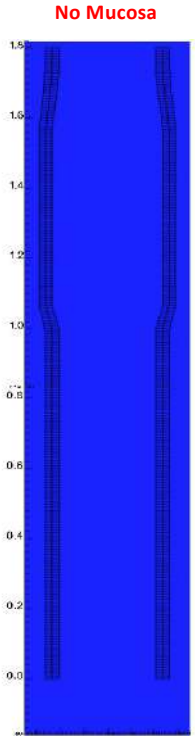




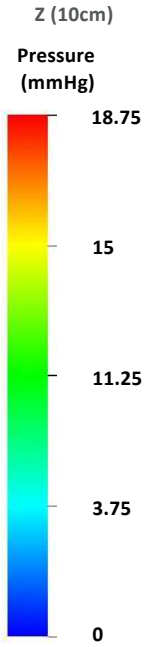
Bridging Physiologic Data and Machine Learning In-Silico Models- Virtual Esophagus

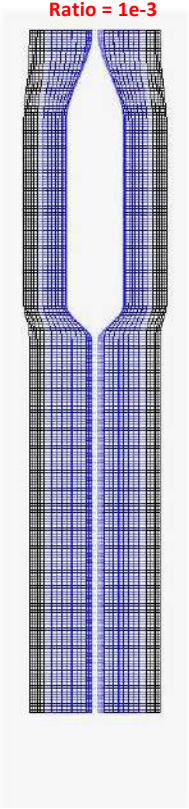


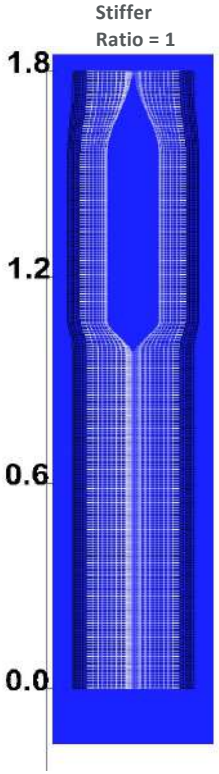


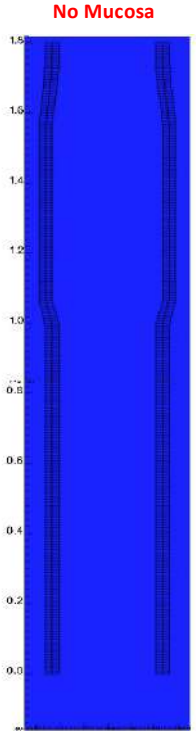


Bridging Physiologic Data and Machine Learning In-Silico Models- Virtual Esophagus



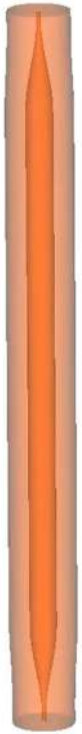






Normal esophagus with EGJ tone

PEP; both ends cosed

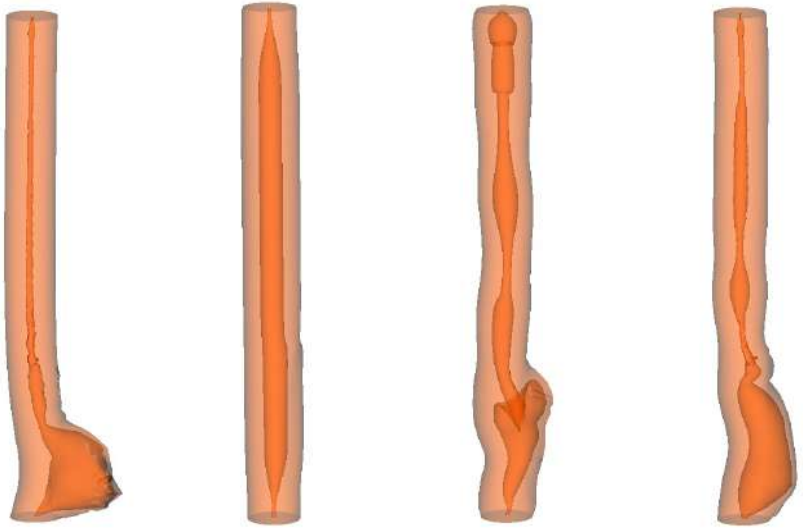


Using In-Silico Models- vEsophagus™

Testing effects of abnormal pathophysiology on function

vEsophagus- inputs are:

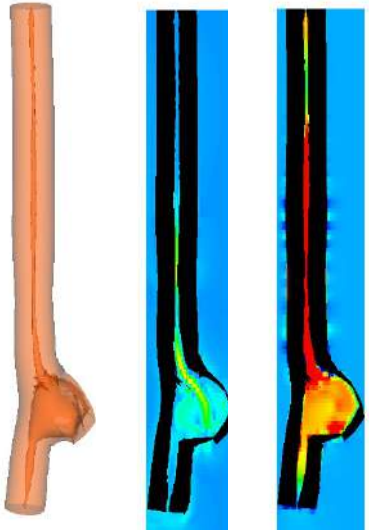
myotomy length and contractile pattern



NL Peristalsis | Absent Contractility | PEP Type II | Spams Type III

Full thickness myotomy

Standard 6 cm- with residual EGJ Tone



Esophageal Function Testing
State of the Art

- The next 5 years will see an explosion of technology and advances in esophageal function testing.
  - CC 5.0- Impedance- *4D HRM, Distention Plots and AIM*
  - High-resolution Manometry- *Intelligent HRIM*
  - FLIP-Panometry- *Intelligent FLIP*
  - **In-silico modeling and Hybrid Physics Based Diagnostics**
    - vEsophagus
    - FLIP-Mech