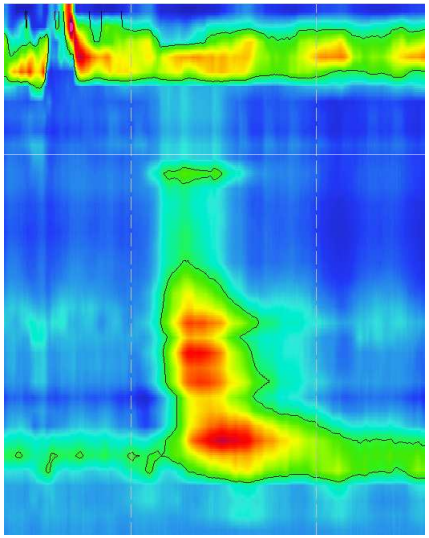
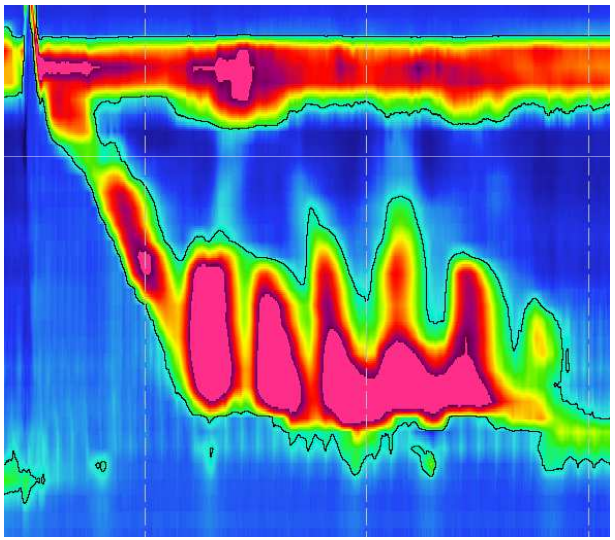
Pathophysiology and histopathology of hypercontractile disorders





Sabine Roman

Digestive Physiology

Hospices Civils de Lyon – Université Claude Bernard Lyon I

Disclosure

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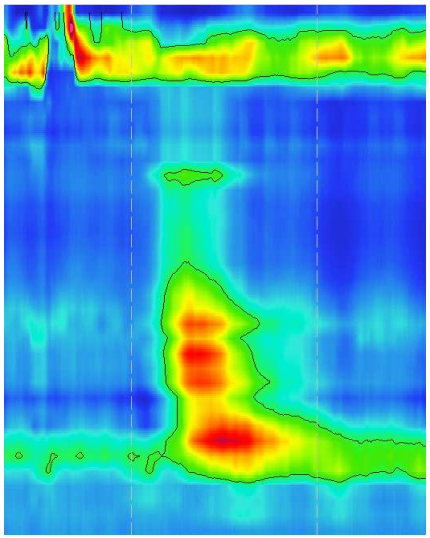
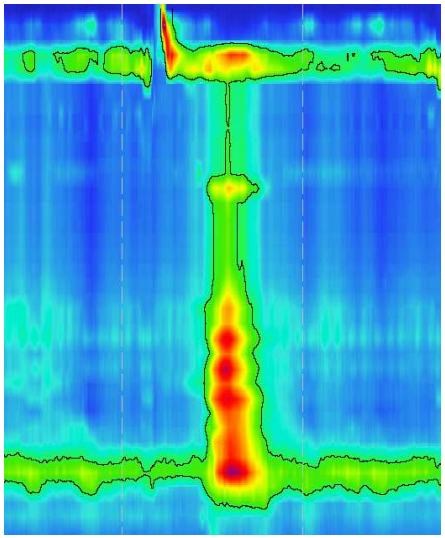
- Research support: Crospon, Diversatek Healthcare
- Travel grant: Biocodex

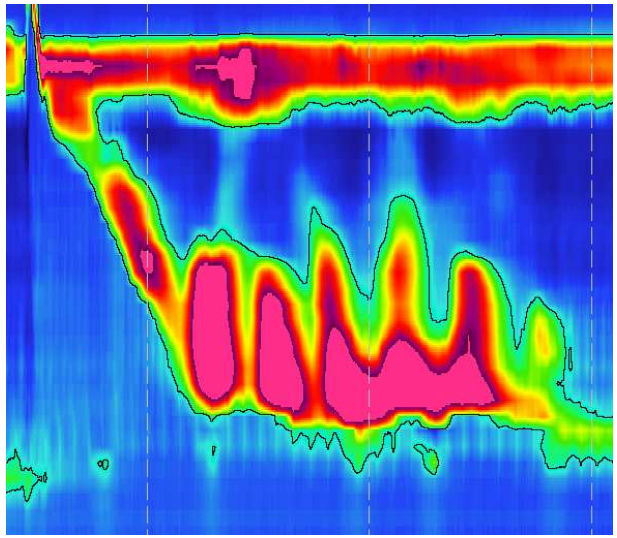
Hypercontractile disorders

- Rare
- Distal esophageal spasm, type III achalasia
- Jackhammer esophagus (nutcracker esophagus)

- Might be idiopathic or associated with EGJ outflow obstruction, medications, eosinophilic esophagitis…







Kahrilas et al, Neurogastroenterol Motil 2017

Esophageal contraction

- Timing of peristalsis (distal smooth muscle esophagus)
  - mediated via excitatory (cholinergic) and inhibitory (nitric oxide) myenteric plexus neurons

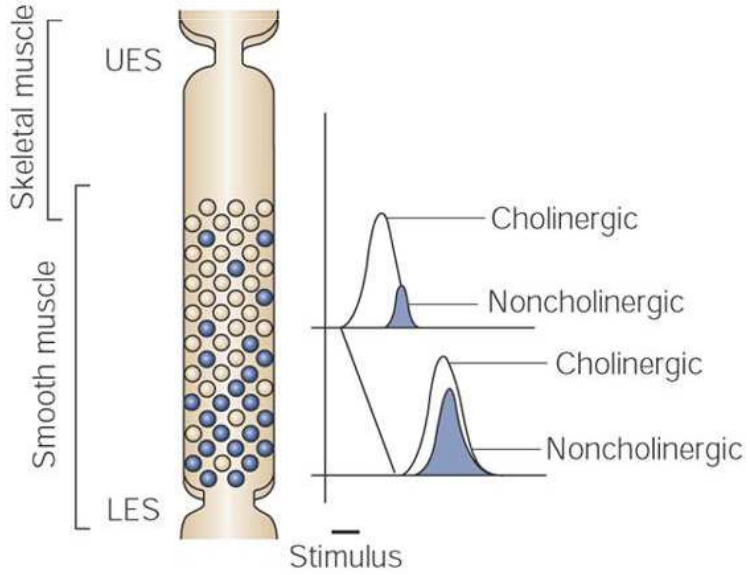
- Neural gradient
  - Excitatory innervation ○

decreases gradually in the distal part

  - Inhibitory innervation ●

increases distally along the esophagus

Latency of the contraction increases distally



Behar & Biancani, Gastroenterology 1993
Goyal & Chaudhury, J Clin Gastroenterol 2008

Pathophysiology

- Timing of peristalsis (distal smooth muscle esophagus)
- mediated via excitatory (cholinergic) and inhibitory (nitric oxide) myenteric plexus neurons

Excitatory (Ach) pathway	Inhibitory (NO) pathway

Behar & Biancani, Gastroenterology 1993
Goyal & Chaudhury, J Clin Gastroenterol 2008

Pathophysiology

- Timing of peristalsis (distal smooth muscle esophagus)
- mediated via excitatory (cholinergic) and inhibitory (nitric oxide) myenteric plexus neurons

Inhibitory (NO) pathway

Excessive cholinergic stimulation

Jackhammer esophagus

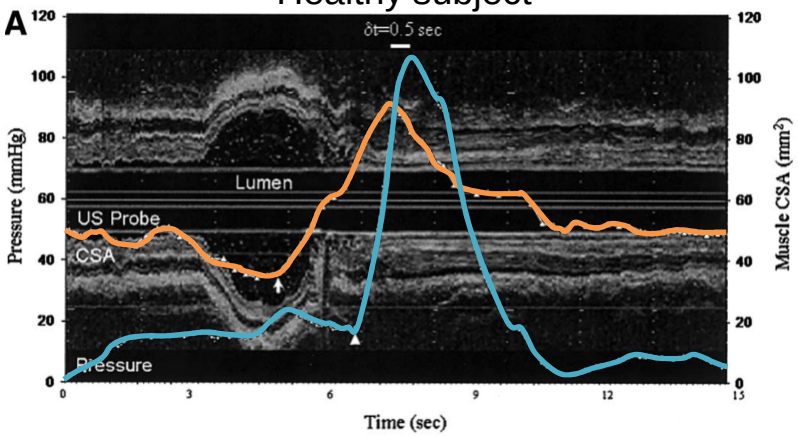
Behar & Biancani, Gastroenterology 1993
Goyal & Chaudhury, J Clin Gastroenterol 2008

Excessive cholinergic stimulation

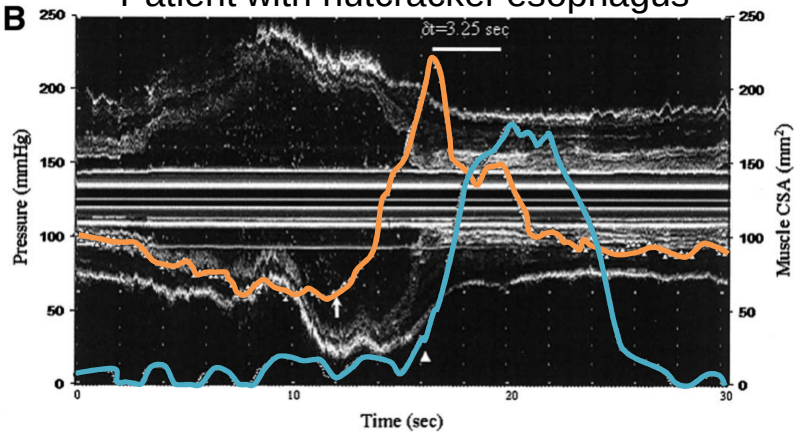
Healthy subjects n=5
Patients with nutcracker esophagus n=10
Measurements 2 and 10 cm above the LES

- ✓ *High frequency intraluminal ultrasound (HFIU) → Changes in muscle cross sectional area (CSA) → marker of* ***longitudinal muscle contraction***
- ✓ *Manometry → Intraluminal pressure → marker of* ***circular muscle contraction***

Healthy subject



Patient with nutcracker esophagus

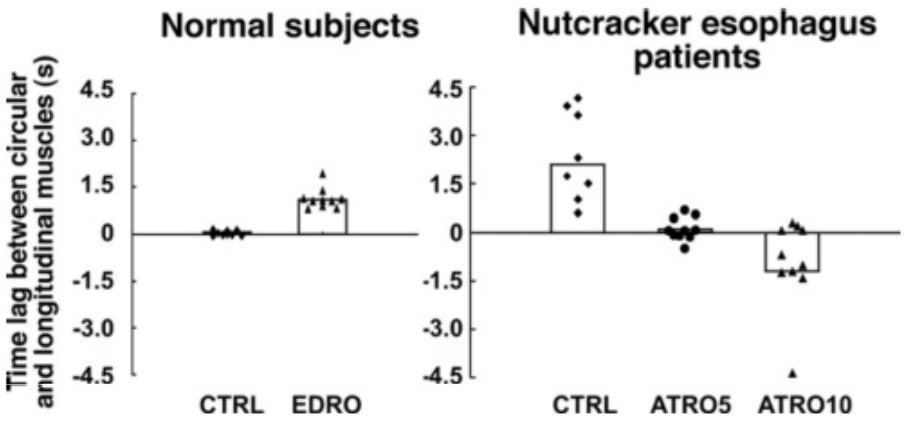


Asynchrony between circular and longitudinal muscle contraction in patients with nutcracker esophagus

Jung et al, Gastroenterology 2005

Excessive cholinergic stimulation

Healthy subjects n=10
Patients with nutcracker esophagus n=10
Measurements 2 cm above the LES
- ✓ *High frequency intraluminal ultrasound*
- ✓ *Manometry*



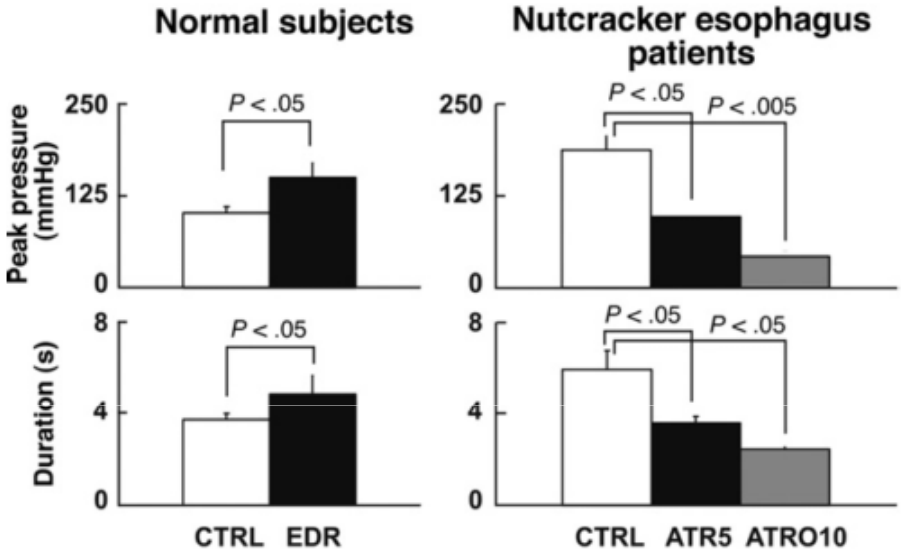
- Healthy controls: cholinomimetic agent induces asynchrony between circular and longitudinal muscle contraction

- Nutcracker esophagus: atropine reverses asynchrony between circular and longitudinal muscle contraction

Korsapati et al, Am J Physiol Gastrointest Liver Physiol 2008
Korsapati et al, Gastroenterology 2008

Excessive cholinergic stimulation

Healthy subjects n=10
Patients with nutcracker esophagus n=10
Measurements 2 cm above the LES
- ✓ *High frequency intraluminal ultrasound*
- ✓ *Manometry*



- Healthy controls: cholinomimetic agent increases contraction amplitude and duration

- Nutcracker esophagus: atropine decreases contraction amplitude and duration

Korsapati et al, Am J Physiol Gastrointest Liver Physiol 2008
Korsapati et al, Gastroenterology 2008

Pathophysiology

- Timing of peristalsis (distal smooth muscle esophagus)
- mediated via excitatory (cholinergic) and inhibitory (nitric oxide) myenteric plexus neurons

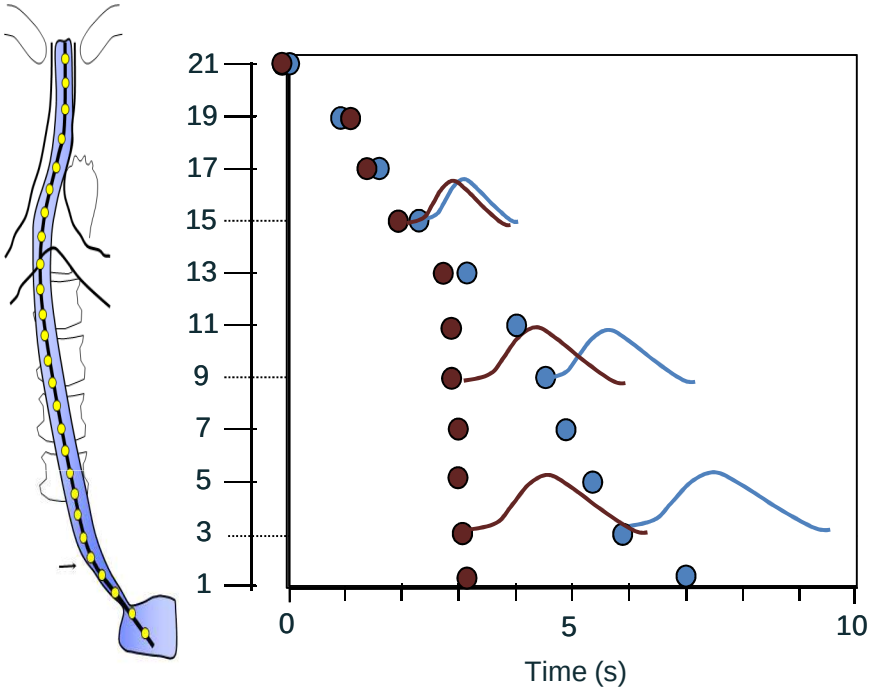
Excitatory (Ach) pathway

Loss of inhibitory neurons function

Distal esophageal spasm
Type III achalasia
Jackhammer esophagus?

Behar & Biancani, Gastroenterology 1993
Goyal & Chaudhury, J Clin Gastroenterol 2008

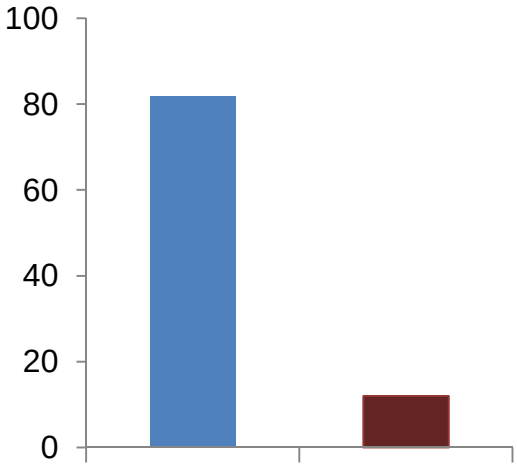
Loss of inhibitory function



Patients with normal peristaltic contractions

Patients with simultaneous contractions

Percentage inhibition induced by 10 wet swallows



- Patients with simultaneous contractions (DES)
  - Shorter distal latency
  - Reduction of inhibition induced by repetitive swallows

Distal latency: manifestation of inhibitory neuron activity that determines the timing of contraction in the distal esophagus

Behar & Biancani, Gastroenterology 1993

Loss of inhibitory function

- Free hemoglobin to scavenge NO in healthy controls
- Induction of simultaneous esophageal contraction
- Inhibition of EGJ deglutitive relaxation

- Role of inhibitory innervation in the genesis of DES and impaired EGJ relaxation

Histology of muscularis propria

Loss of myenteric plexus ganglionic cells in achalasia
But less likely complete in type III achalasia than in type I or II

Loss of interstitial cells of Cajal in achalasia and DES?

Murray et al, Gastroenterology 1995
Sodikoff et al, Neurogastroenterol Motil 2016
Nakajima et al, Neurogastroenterol Motil 2017

Alteration of neural control

- Patients with jackhammer esophagus (n=83)
- ✓ Multiple rapid swallow (MRS) and rapid drink challenge (RDC) test

- ➢ Abnormal motor inhibition during MRS 48% of patients with JE (vs 29% of controls, p=0.29)

- ➢ Mean DCI after MRS lower than after single swallow in patients with JE → 66% of patients with JE have no contractile reserve

- ➢ Obstructive pattern on RDC 25/34 JE patients (74%)

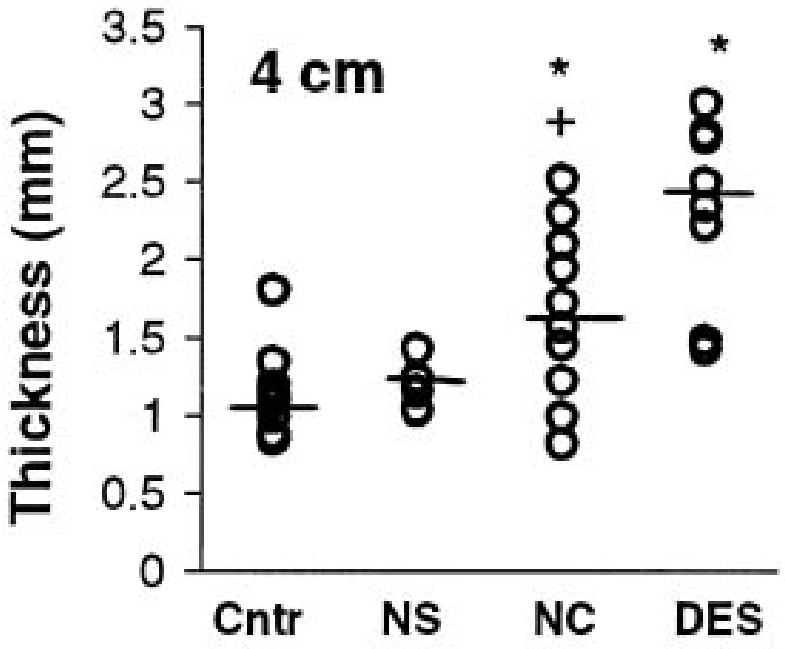
Mauro et al, Am J Physiol Gastrointest Liver Physiol 2019

Relation with muscle thickness

NOS knockout mice → increased muscularis propria thickness
Lack of inhibitory innervation might be associated with increased muscularis propria thickness?

- High frequency intraluminal ultrasound
- ✓ 10 controls
- ✓ 11 nutcracker esophagus
- ✓ 8 DES
- ✓ 7 non specific disorders

Increased esophageal smooth muscle thickness in DES and nutcracker esophagus patients



Mashimo et al, Gastroenterology 2000
Pelhivanov et al, Am J Physiol Gastrointest Liver Physiol 2002
Dogan et al, Am J Gastroenterol 2007

Relation with muscle thickness

- Increased esophageal muscularis propria thickness

- 62 patients with esophageal motility disorders
- Standard radial endosonography

	Wall thickness (mm) Median (95%CI)
Achalasia I (n=4)	2.1 (2.1-2.2)
Achalasia II (n=12)	5.9 (5.8-6.0)
Achalasia III (n=11)	6.1 (5.5-6.7)
EGJOO (n=20)	6.7 (6.6-6.8)
EGJOO + jackhammer (n=3)	6.1 (6.0-6.2)
DES (n=2)	8.1 (8.0-8.2)
Jackhammer (n=9)	7.4 (7.2-7.5)

Pelhivanov et al, Am J Physiol Gastrointest Liver Physiol 2002
Dogan et al, Am J Gastroenterol 2007
Krishnan et al, Neurogestroenterol Motil 2014

Pathophysiology

Distal esophageal spasm
Type III achalasia

Jackhammer esophagus

- Idiopathic motility disorders
- Imbalance inhibitory / excitatory pathways
- Increased muscularis propria thickness
- Histology?

Loss of myenteric plexus ganglionic cells
Loss of interstitial cells of Cajal in achalasia and DES?

Inflammation?

Sodikoff et al, Neurogastroenterol Motil 2016
Nakajima et al, Neurogastroenterol Motil 2017

Inflammation

- Achalasia:

✓ Degeneration and significant loss of nerve fibers associated with predominant T-cell lymphocytic infiltrate around the myenteric plexus

- Non achalasia primary motor disorders

14 DES, 22 nutcracker esophagus, 33 IEM and 70 controls (GERD referred for pre-operative manometry)

✓ Predominantly ***focal peripapillary lymphocytic esophagitis*** (exclusion of reflux esophagitis): 36% of DES, 45% of nutcracker esophagus vs 21% of patients with IEM and 4% of controls

Raymond et al, Histopathology 1999
Putra et al, Am J Surg Pathol 2016

Role of eosinophilia

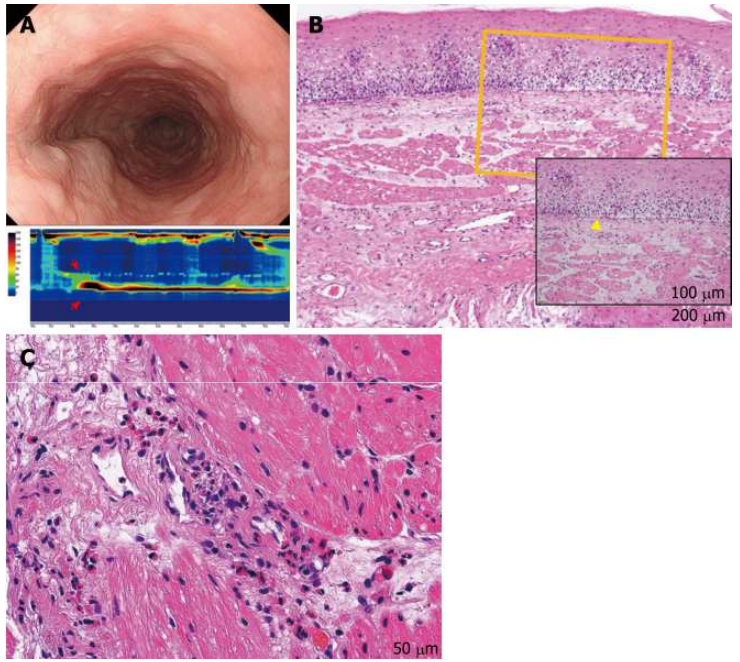
- Infiltration of the muscle layer with Eo cells

in patients with jackhammer esophagus and nutcracker esophagus

(biopsies during POEM or jumbo forceps biopsies)

No eosinophil in the epithelium

- No overexpression of eotaxin 3, IL 5 and IL 13 contrary to “epithelial” EoE



- Subepithelial form of eosinophilic esophagitis
- All types of motility disorders (including achalasia, DES, jackhammer) observed in patients with (epithelial) EoE

Sato et al, World J Gastroenterol 2017
Nakajima et al, Neurogastroenterol Motil 2017
Schoepfer et al, Am J Gastroenterol 2018
Roman et al, Neurogastroenterol Motil 2011

Pathophysiology

- Secondary disorders

- Eosinophilic esophagitis
- Medications
- EGJ obstruction
- GERD

Medications

- Anticholinergic medications

Excessive cholinergic stimulation

Jackhammer esophagus

40 patients with hypercontractile esophagus (HE) (high DCI)
33 controls

→Patients with HE more likely on anticholinergic medications than controls at the time of HRM (75% vs 39%, $p<0.005$)

→**Anticholinergics:**

- Cause of motility disorders?
- Prescription because of symptoms secondary to esophageal hypercontractility?

Schupack et al, Neurogastroenterol Motil 2017

Medications

- Opiates

Association with
- Decreased LES relaxation
- Increased IRP
- Decreased distal latency
- Increased amplitude of esophageal contractions (conventional manometry)

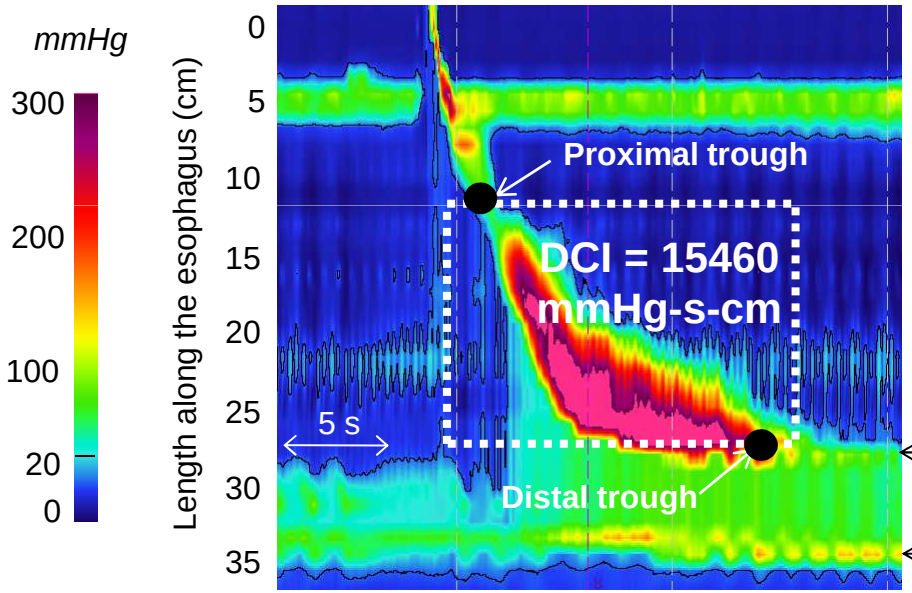
121 chronic opioid users

High resolution manometry (CC 3.0)	ON medication (n=66)	OFF medication (n=55)	p
EGJ outflow obstruction	27%	7%	0.004
Type III achalasia	11%	0	0.015
DES	45%	36%	0.266
Jackhammer esophagus	12%	5%	0.341

Penagini et al, Gastroenterology 1997
Kraichely et al, Aliment Pharmacol Ther 2010
Ratuapli et al, Am J Gastroenterol 2015

Role of EGJ obstruction

- Experimental EGJ obstruction caused esophageal muscle hypertrophy and hyper-excitability in animals



- Gastric banding = "model" of EGJ obstruction in humans

→ Band inflation induces hypertensive contractions

- Increased distal contractile amplitude in EGJ obstruction (functional vs mechanical)

Mittal et al, Am J Physiol Gastrointest Liver Physiol 1991
Conklin et al, Gastroenterology 1991
Burton et al, Obes Surg 2009
Gyawali et al, Neurogastroenterol Motil 2011

Role of acid exposure

- Acid perfusion in patients with non cardiac chest
  - Multipeaked, repetitive, spontaneous or simultaneous contractions

- Proven GERD in around 40% of patients with jackhammer esophagus

but symptoms improvement not related with PPI treatment

Crozier et al, Am J Gastroenterol 1993
Mallet et al, Dig Liv Dis 2016
Kristo et al, Sci Rep 2018

Conclusions

- Hypercontractile disorders
  - Alteration of neural control
  - Imbalance between excitatory and inhibitory pathway

- Increased esophageal muscle thickness
- Inflammation and loss of myenteric plexus

- Idiopathic
- But also secondary to
  - Eosinophilic esophagitis
  - Opiates
  - EGJ obstruction
  - GERD