Neuromuscular diseases of the stomach
GASTROPARESIS

INSELSPITAL
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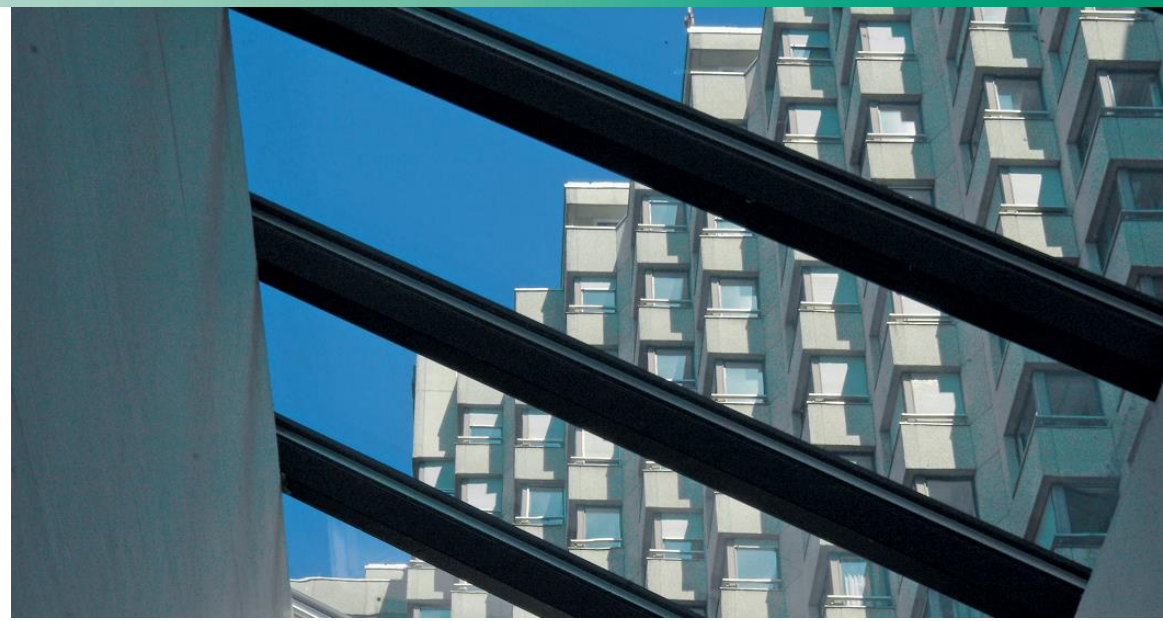
BERN UNIVERSITY HOSPITAL



Update 2022

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Bible Class 26.1.2022

Content – Learning Objectives

- **Physiology of gastric motility and its regulation**
- **Causes/ pathophysiology of gastroparesis (incl. Neuromuscular)**
- **Diagnostic approach (methods, read-outs)**
- **Treatment goals, options, drugs, interventions**
- **Outlook**

……start with Epidemiology, Impact on individual patient

Epidemiology: Gastroparesis

It is frequent just seek – test

Prevalence:

ca. 2% (teste

e.g. 5 Mi

femal e: M 20% - F 80%

Olmsted county):

7.7) per 100,000 person-years

6-fold increase in dischage diagnosis in US 1997 to 2013

Standardized prevalence of gastroparesis was 267.7 cases per 100 000 persons on July 1, 2018

Prevalence (95% CI)[a]	Adults with gastroparesis (n = 32 010)	Adults with diabetic gastroparesis (n = 13 180)	Adults with idiopathic gastroparesis (n = 2543)
Standardized prevalence	267.7 (264.8–270.7)	101.4 (99.7–103.1)	24.8 (23.9–25.8)

[a]Prevalence calculated p sons, and standardized by age, sex and geographic region. C l.

major source of

- healthcare costs
- self-costs to patients
- loss of work productivity

associa

- si ecrease in quality of life
- ocial comorbidities:
  ty and depression
  eight loss/ decreased life expectancy ?

Costs per gastroparesis patient In US annually 35.000 US-Dollar

Jung HK et al. Gastroenterology. 2009;136(4):1225–33.

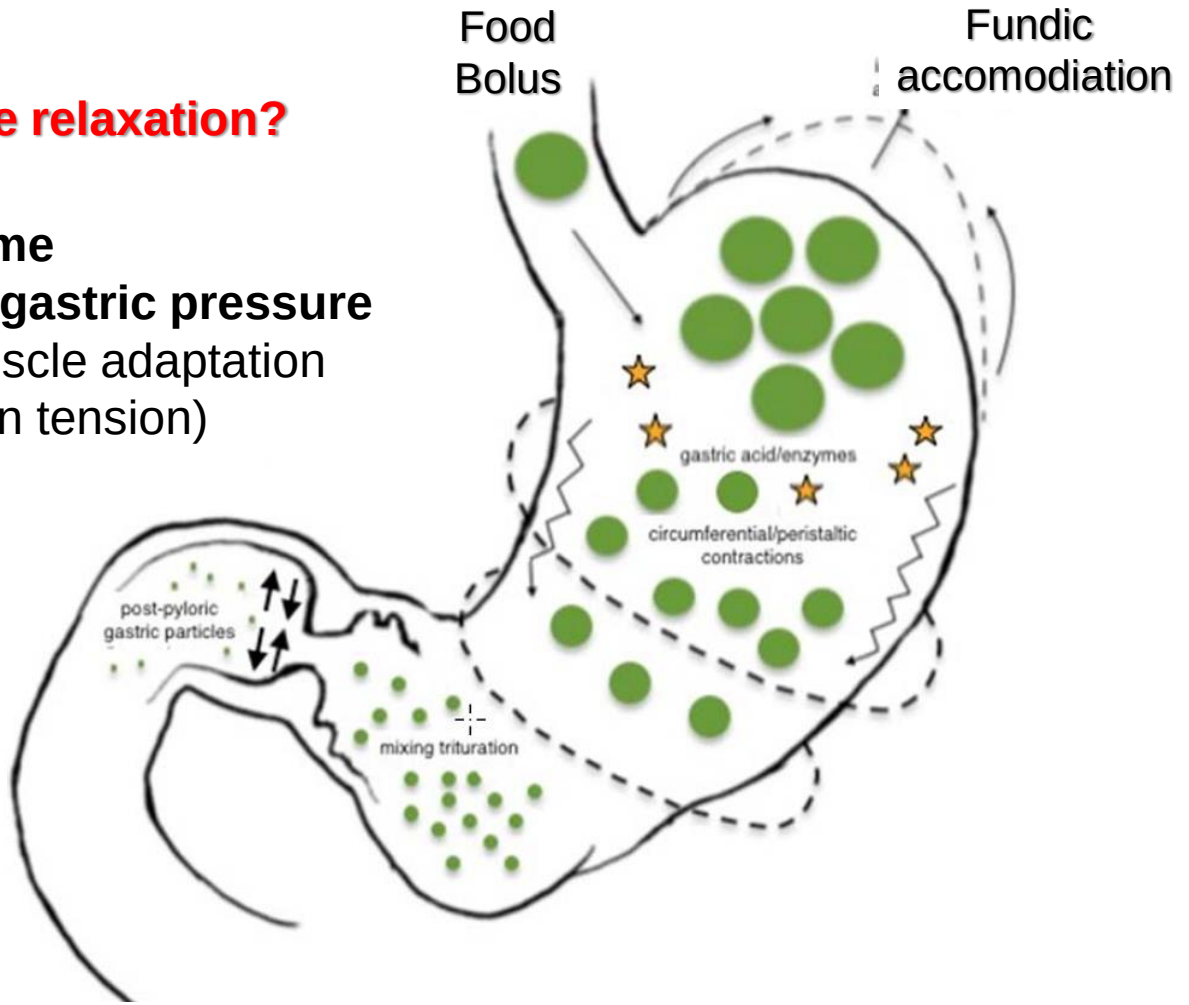
Camillieri et al. Gastroenterology 2022

Physiology Gastric Motility

Function of different portions of the stomach…

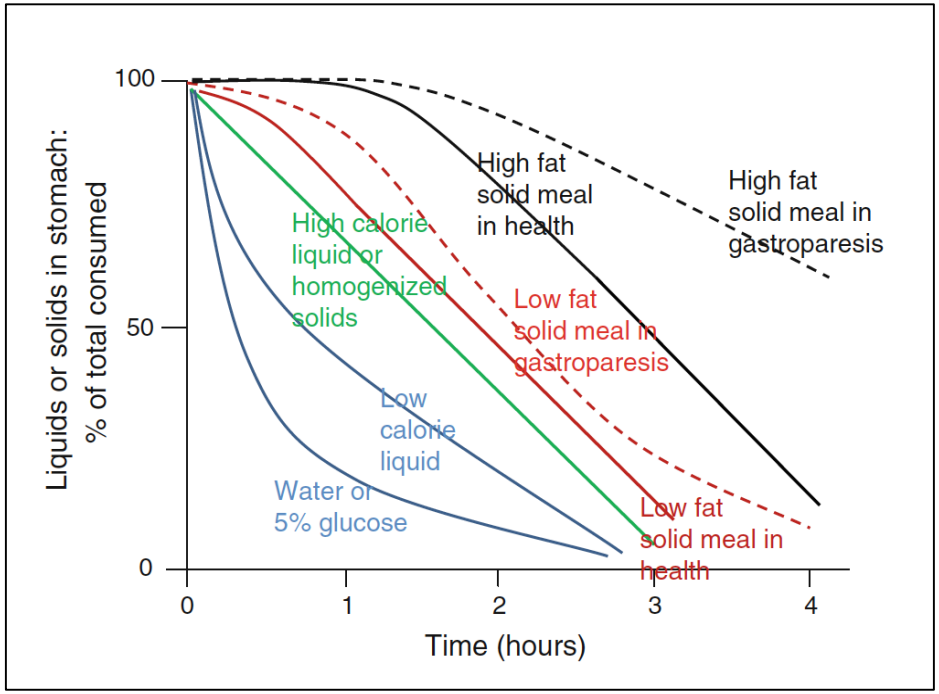
What is recepitive relaxation?

Up to 1 liter volume
No increase intragastric pressure
Due to smooth muscle adaptation
(without increase in tension)



Physiology Gastric Emptying: Kinetics, Phases…

3 Phases of gastric peristalsis



Camilleri & Shin Dig Dis Sci 2013; 58:1813–1815

Lag phase:

Trituration content to particels <2 mm

Linear phase: **depends on**

energy content

Fat and fibres slow down

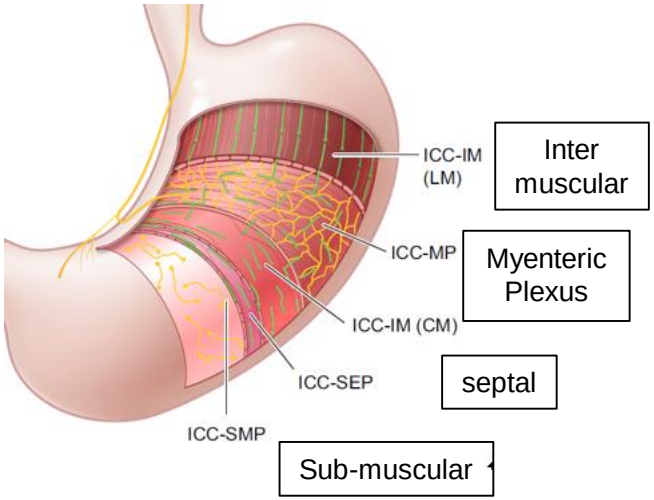
Migrating Motor Complex (MMC)

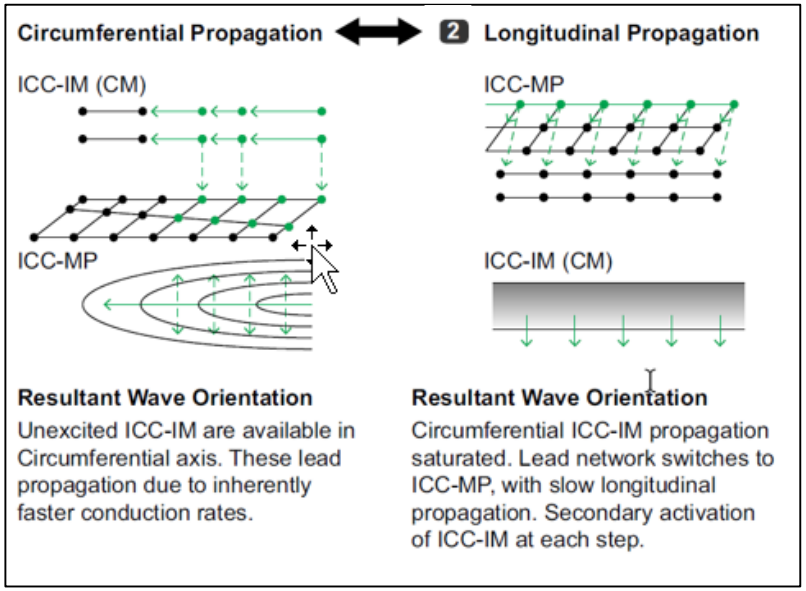
Interdigestive phase:

Emptying remnants (non-digestibles)

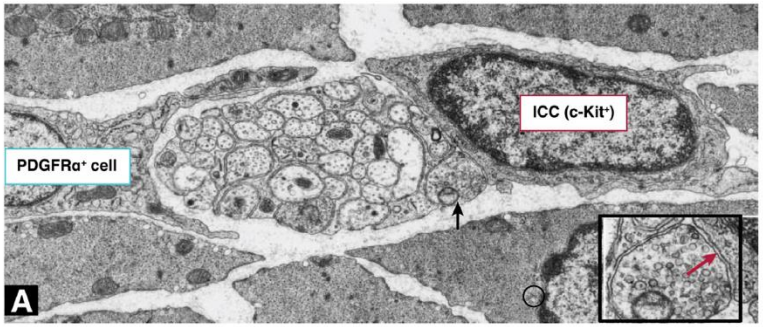
Up to 3 strong waves/minute

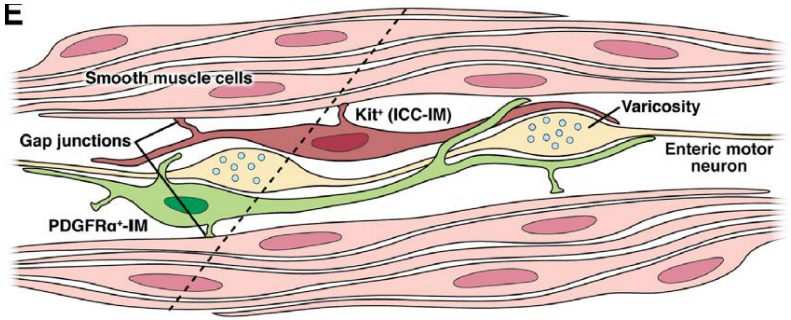
Types of interstitial cells Cajal (ICC):





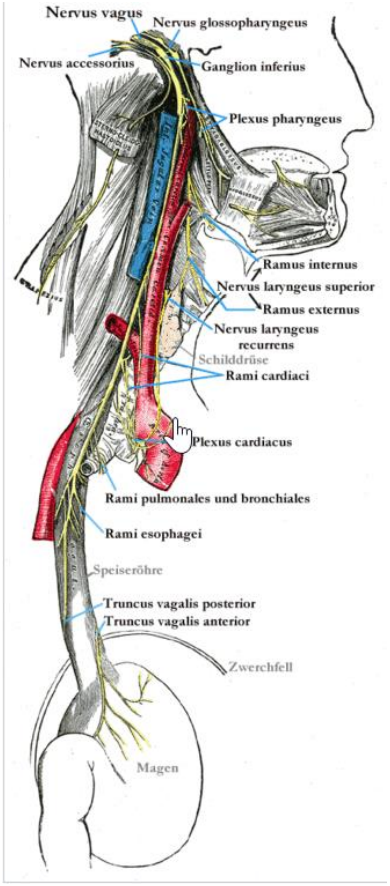
Syncytium: Smooth muscle – ICC-PDGFR-cell forming one network

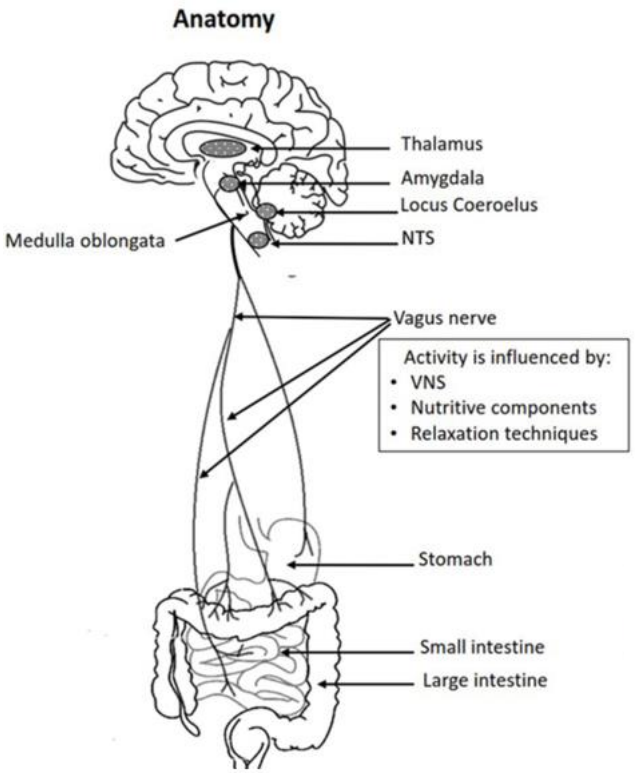


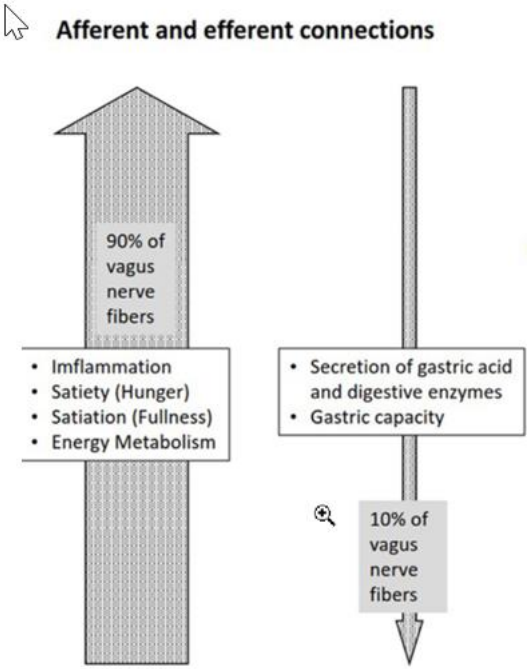


ICC are in close proximity to nerve endings (extrinsic input)

What is the single most important nerve for GI motility ?

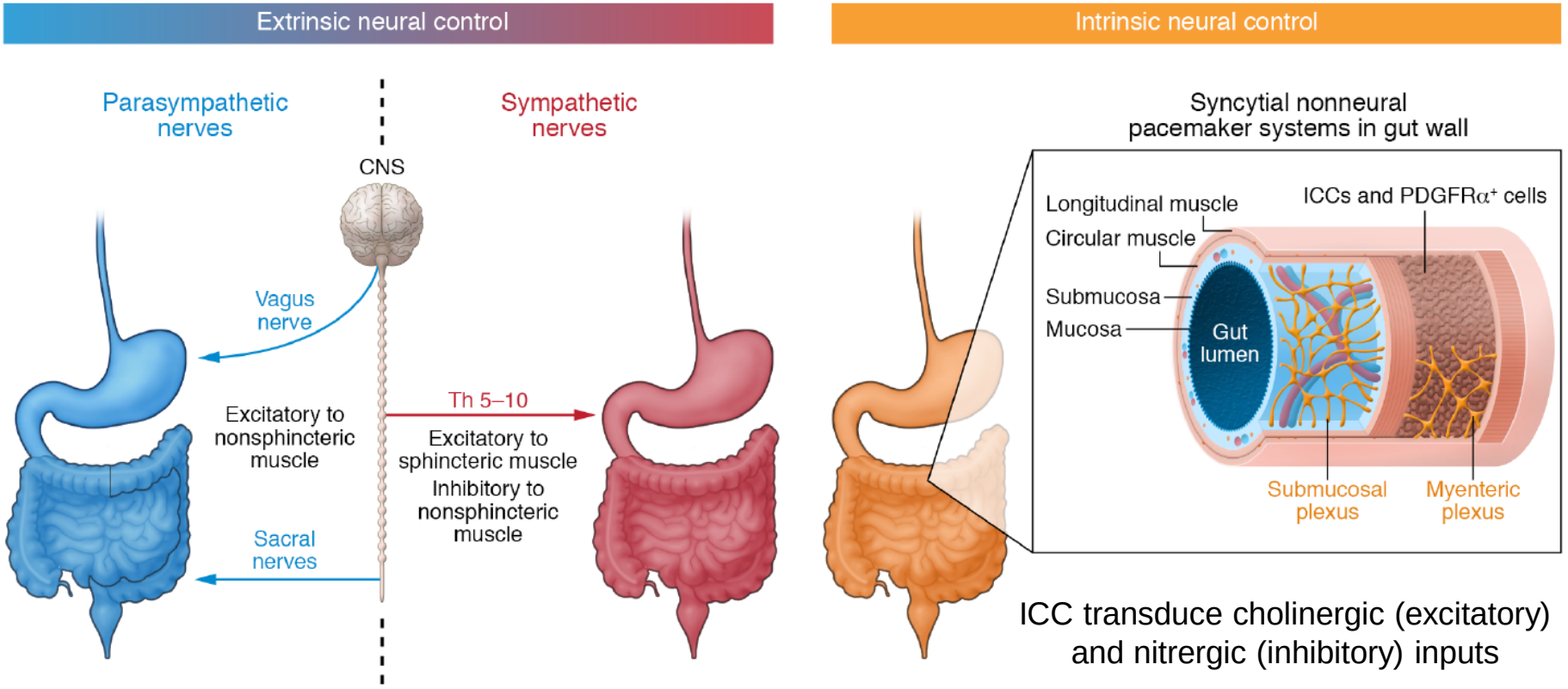






«vagari» = «umherschweifen»

Nerval Regulation of Gastrointestinal Motility

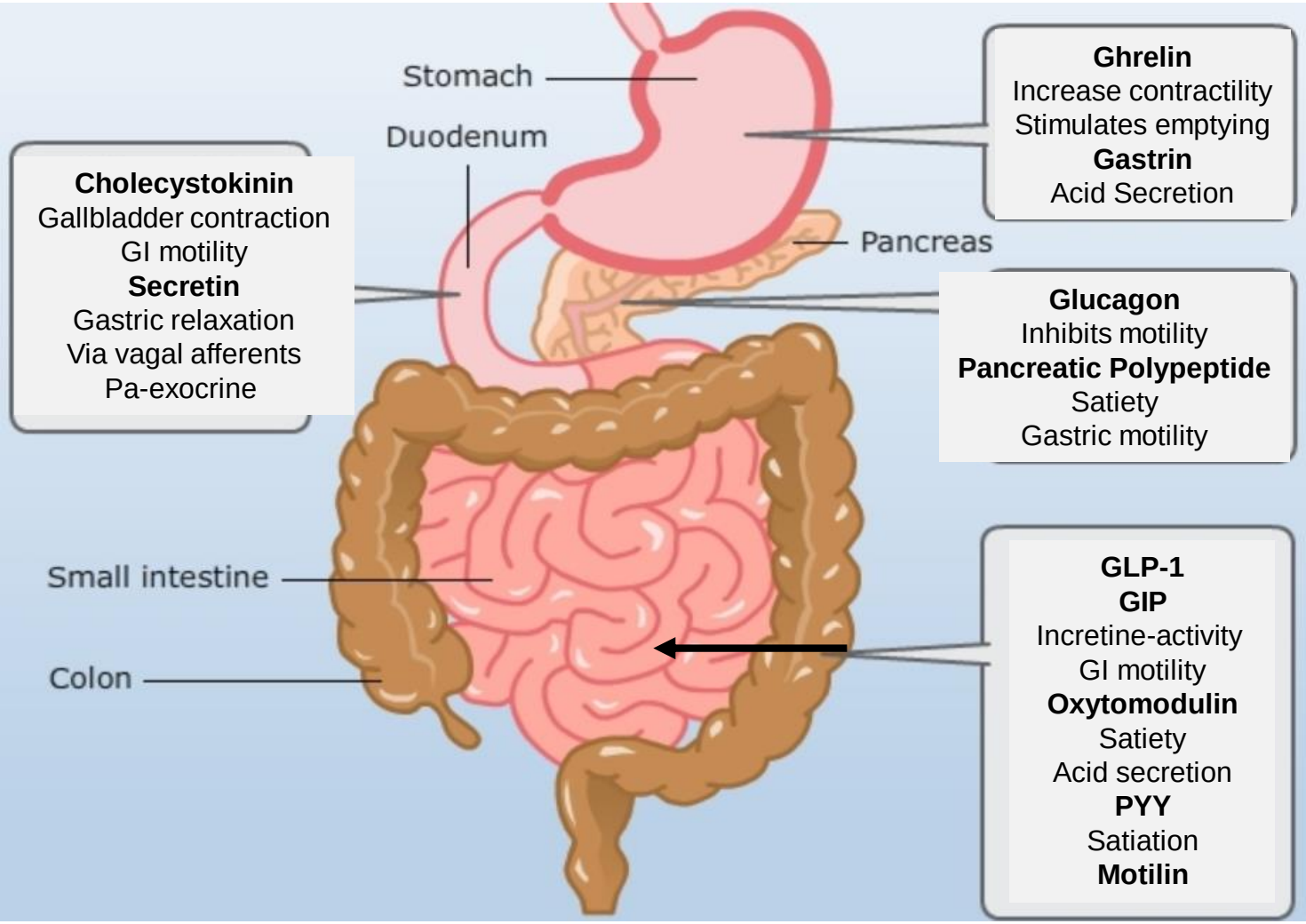


ICC transduce cholinergic (excitatory) and nitrergic (inhibitory) inputs

Vagal/cholinergic
Generaly excitatory to SMC
(positive inotrop, chronotrop)
except fundus (relaxation)

SNS/adrenergic:
Generally inhibitory to muscle layer (except sphincter)
(via intrinsic inhibitory ENS: VIPergic, NO-ergic..

Hormones involved in regulating gastric motility ?



Pathophysiology

Gastroparesis is defined as ….

(set of) symptom/s that is (are)
associated with delayed GE
in the absence of mechanical obstruction
with severely disturbed gastric motor function
and being chronic (at least 3 months)

Cardinal-Symptoms: Nausea and vomiting

Dyspeptic symptoms:
postprandial fullness
early satiation
epigastric pain
Bloating, belching

are often present
in gastroparesis
DD Dyspepsia

Grover M, et al. Gut 2019;68:2238–2250

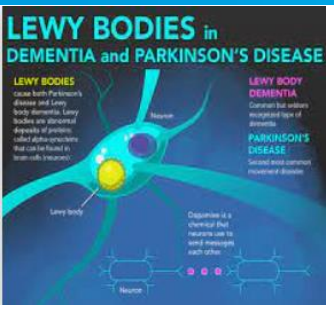
Neurological -/Brain-diseases causing Gastroparesis ?

Brain-diseases (e.g. Parkinson)

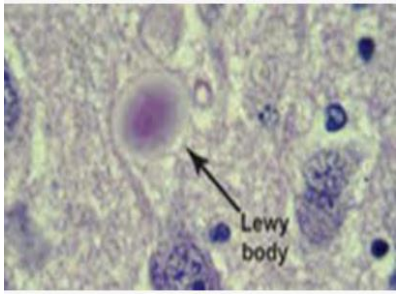
Autonomic System Degenerations

Spinal Cord lesions

Peripheral Neuropathies (e.g. Diabetic)



M. Parkinson and gastric dysmotility/-paresis



Braak hypothesis: pathogen reaches gut, initiates pathology + spreads to CNS

PPh: accumulation abnormal inclusions: α-synuclein (Lewy neurites) in the ENS*

ICC not altered, ghrelin-levels lower, vagal dysfunction proposed→

Total vagotomy associates with lower prevalence Parkinson

Gastroparesis in 45% (up to 70%) of Parkinson -cases

But leading often dysphagia, constipation, defecation-problems, sialorrhoe..

GI symptoms can precede motor dysfunction (akinesia) many years (+ *)

Liu et al. Neurology 2017; Cersosimo J Neurol 2013; Rietdijk CD, et al. *Front Neurol*. 2017;8:37.

Brain diseases: gastric dysmotility/-paresis ?

Stroke (mainly dysphagia, constipation) but

bilateral posterior inferior cerebellar artery territory infarct causes severe gastroparesis

Head Injury: usually transient delay in gastric emptying

Brain Stem Lesions: vagal «relais» in

dorsal motor nucleus vagus (DMV), Nucleus tractus solitaries (NTS: afferent vagal)

Alzheimer disease

Dementia (drugs inhibiting acetylcholin-esterase: e.g. donepezil)

Multiple System Atrophy (MSA): dysfunctional autonomic nervous system

Amyotrophic Lateral Sclerosis (ALS)

Cliff et al. Clin Neuro Neurosurg 2012

Spinal cord lesions and peripheral neuropathies associate with gastroparesis…..

Acute polyneuropathies (e.g. infectious, Guillan-Barre-Syndrome, HSV, Covid….)

Chronic polyneuropathies: Diabetes mellitus

Paraneoplastic polyneuropathies:

mainly small-cell carcinoma of the lung or

pulmonary carcinoid or neuroendocrine tumors

Autoimmune Neuropathies: e.g. ganglion-receptor-binding auto-antibodies

HIV-Polyneuropathy

Porphyria

Neurofibromatosis

Autonomic system degenerations are ?

- **Pandysautonomia (SNS + Vagus; cases EBV/CMV-triggered)**
- **Familial Dysautonomia (Riley-Day-Snydrome)**
- **Pure autonomic failure (=loss peripheral adrenergic innervation)**
- **Postural orthostatic tachycardia syndrome (POTS)**
- **Myasthenia gravis (failure neuromuscular junction transmission)**

Muscular disease causing dysmotility and/or gastroparesis

- **Duchenne + Becker muscular dystrophy**
- **Poly-/Dermatomyositis**
- **Hollow visceral myopathy**
- **Mitochondrial Encephalomyopathy**
- **Myotonic dystrophy**

Low-amplitude Contractions

Diagnostic via EMG (skelettal) Biopsy (peripheral)

Drugs contributing to gastroparesis are ?

- Anticholinergic agents (diphenhydramine, ..)
- Adrenergic agents (beta-agonists,…)
- Ca-channel blockers
- Incretins (GLP-1/GIP- analoga)
- Opioids
- Levo-Dopa
- Lithium
- Alcohol
- Cyclosporine
- …..

PPI
can slow gastric emptying

STOP
if not needed/GERD

Hasler WL, Clin Gastroenterol Hepatol. 2019

Etiology Gastroparesis

Diabetic Gastroparesis (30%)

- Usually after >10 J in type II
- Type I > II: 5% vs. 1%
- vs. 0.2% non-diabetic contr
- Hyperglycemia directly slows gastric emptying
  even within physiol range
  (hypoglycemia accelerates gastric emptying)

- poor glycemic control = independent risk factor for upper GI symptoms

Idiopathic Gastroparesis (30%)

- Overlap functional Dyspepsia

- Inflammatory ?
- DD: EPS more often pain
- DD: PDS overlapping

Symptoms related to dysmotility in ca. 15%

Others (40%):

Postsurgical (Vagal Dysfunction)*
Drug-induced (Opiate etc.)
Connective tissue disease/
Sclerodermia
Lupus erythematodes
Neurological diseases
Brain lesions
Hypothyreose
Ischemia
Renal insufficiency
Liver cirrhosis
Anorexia
Paraneoplastic Syndrom
Amyloidosis
……

Choung RS et al. Am J Gastroenterol. 2012

*: Partial gastric resection/vagotomy, bariatric surgery, antirefluxsurgery

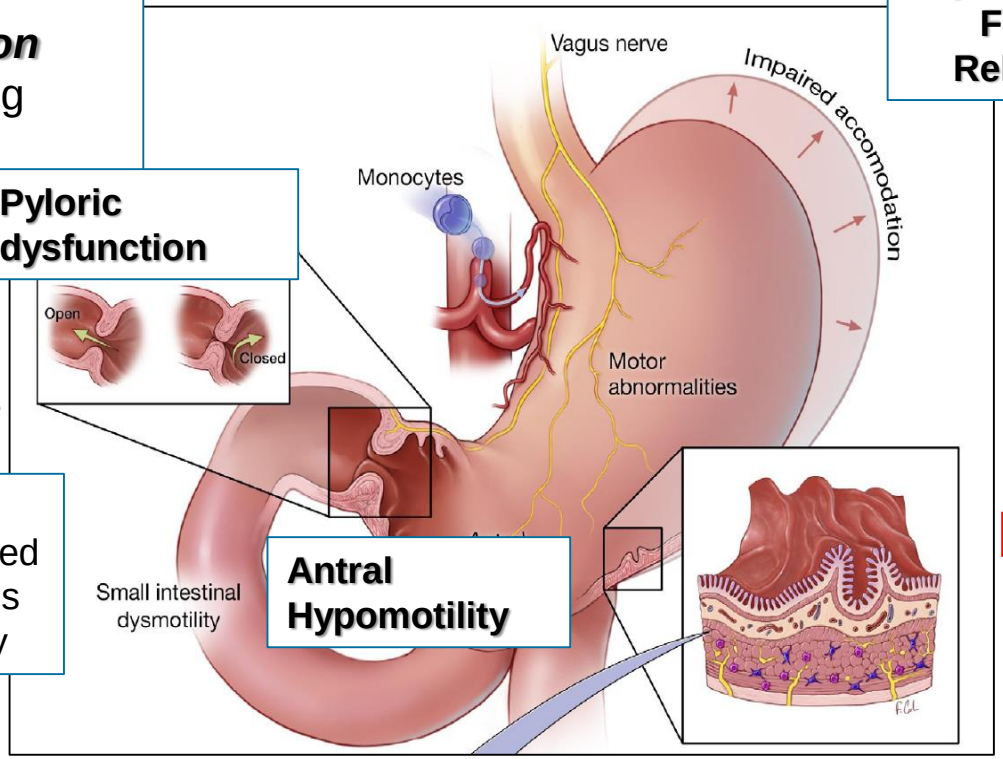
Key pathophysiology in gastroparesis

Gastric compliance NOT altered =
hypersensitivity to stretch/distension
by altered processing in the CNS

Pyloric dysfunction

Prolonged contraction
Increased basal tone
higher contr amplitude

Esophago-gastral Electrical stimuli: altered evoked brain potentials ≈ GI symptom severity



Dysfunctional Fundus Relaxation

Mechanisms

Lelik D et al. NGM 2014; Grover M, et al. Gut 2019;68:2238–2250; Snodgrass P et al. DigDisSci 2019

Pathophysiology: sites and mode of dysfunction

ICC	Nerves	Smooth muscle	Immune cells

• ↓ numbers in gastric body and antrum (antrum>body).[52, 74] Absence of well-defined myenteric plexus of ICC.[52]
• Apoptotic bodies, intracytoplasmic vacuoles, extended rough endoplasmic reticulum, swollen mitochondria.[53]
• ↑ ICC-ICC, ICC-Nerve separation.[53]
• Altered Ano-1 expression and Ano-1 variant proportions in DG which affect ICC electrical activity.[79]
	• *Vagal dysfunction*
	  • Gastric hypo-/atonia on imaging. Blunted pancreatic polypeptide response and gastric secretion upon sham-feeding.[48]
	• Histological changes in myelinated and unmyelinated fibres.[49]
	• *ENS changes*
	  • ↓ inhibitory (nNOS, VIP) and excitatory (Ach, SP) fibres in only a small subset of patients.[52]
	• Loss of synaptic vesicles, thickened basal lamina and fibrosis around nerves (IG>DG).[53]
		• Case reports showing smooth muscle degeneration, fibrosis, collagenous thickening with eosinophilic inclusion bodies (pylorus>body)[151, 152]
		• Reduced smoothelin expression in ~20% of patients. Absence of immunochemical and ultrastructural changes in majority of patients.[52]
		• ↓ FOXF1 and FOXF2. ↑ MYH11, MYLK1 and ACTA2 mRNAs in smooth muscle tissues obtained from IG.[83]
			• ↓ CD206 positive anti-inflammatory macrophages.[74]
			• ↑ proinflammatory macrophage gene expression in IG.[88]
			• Transcriptomic and proteomic pathway analysis showing macrophage based immune dysregulation.[88]
			• Long GT alleles in HMOX1 gene in DG which associated with worse nausea symptoms.[87]

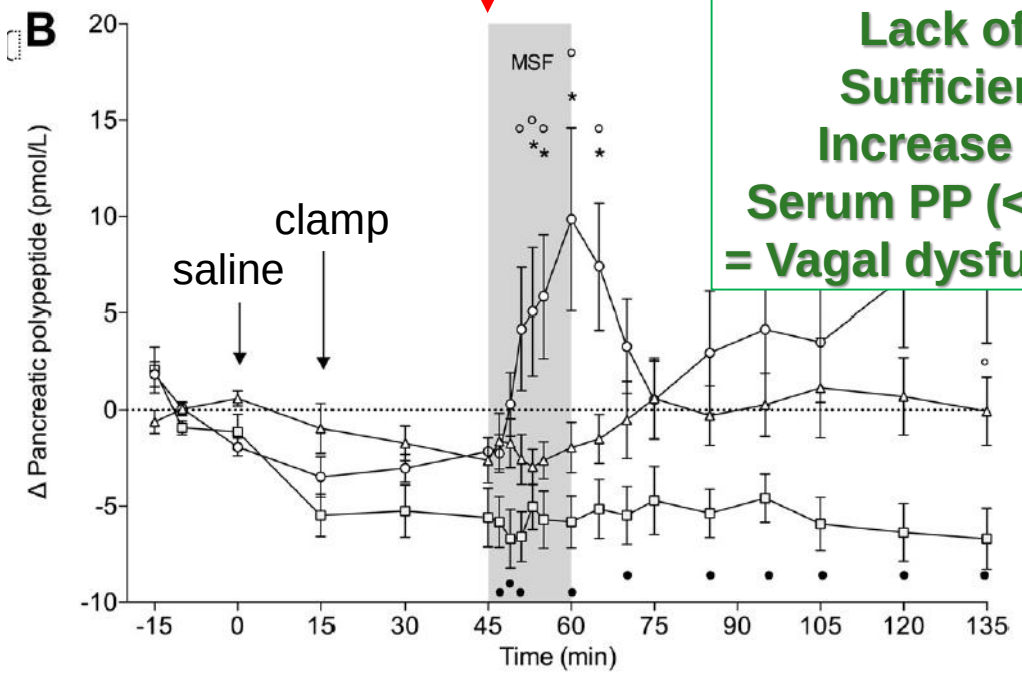
Ach: Acetylcholine; Ano-1: anoctamin; DG: diabetic gastroparesis; ENS: enteric nervous system; ICC: Interstitial cells Cajal; IG: idiopathic gastroparesis; nNOS: neuronal nitric oxide synthase; SP: substance P; VIP: vasoactive intestinal peptide

Diagnostic

Can we measure visceral vagal nerve function ?

Pancake
Jam
Eggs
Juice
Coffee
….
No swallow

Sham-feeding test = «Chew and Spit» protocol



°SAL+CLA+MSF vs. SAL+CLA and ATR+CLA+MSF, P<0.05
*SAL+CLA+MSF vs. t=45 min, P<0.05
•ATR+CLA+vs. SAL+CLA and SAL+CLA+MSF, P<0.01

Lack of Sufficient Increase in Serum PP (< 50%) = Vagal dysfunction

Atropin Blocking Vagal transmission

Veedfaldt et al. AJP 2016

Balaji NS et al. Arch Surg 2002

Pankreatisches Polypeptid - Sham feeding test

	Röhrchen Nr.	Abnahmezeit	PP pg/ml
Nullwert 1	1	14:00	74
Nullwert 2	2	14:00	75
Essen Simulation (Pizza)			
Anfang		14:06	
Ende		14:30	
Nach sham-feeding			
15 min	3	14:45	75
30 min	4	15:00	75
45 min	5	15:15	87

Interpretation:

Fehlender Anstieg des Pankreatischen Polypeptids im Serum nach Verabreichung einer Scheinmahlzeit. Damit ergibt sich ein Hinweis auf eine vagale Innervationsstörung des Pankreas.

Gastroparesis Cardinal Syptom Index (GCSI)

		none	Very mild	Mild	Moderate	Severe	Very severe	Sum	Aritheme tic Mean
1.	Nausea	0	1	2	3	4	5		
2.	Retching	0	1	2	3	4	5		
3.	Vomiting	0	1	2	3	4	5		
4.	Stomach fullness	0	1	2	3	4	5		
5.	Not able to finish a normal sized meal	0	1	2	3	4	5		
6.	Feeling extensively full after meals	0	1	2	3	4	5		
7.	Loss of appetite	0	1	2	3	4	5		
8.	Bloating	0	1	2	3	4	5		
9.	Stomach or belly visibly larger	0	1	2	3	4	5		

1-3 = nausea/vomiting

4-7 = post-prandial fullness/ early satiety

8-9 = bloating

Total GCSI Score = _____

> 2.3 = Gastropareseis

Calculation:

Total GSCI score = arithmetic mean of the three symptom subscales

Subscores = arithmetic means of (1-3), (4-7) and (8-9)

Diagnostic work-up suspecting gastroparesis

Upper gastrointestinal endoscopy is mandatory for establishing a diagnosis of gastroparesis

Presence of food in fasting state during endoscopy Is diagnostic for gastroparesis *

An abnormal gastric-emptying test is mandatory for establishing a diagnosis of gastroparesis

* PPV for delayed GE 55% (32%-80%):
latter with risk factors (DM, drugs, neurological disease)

Bi D et al. DigDisSci 2021

UEG Journal (Consensus) 2021; 9:287 ff

Measuring gastric emptying: Methods ?

Scintigraphy:

Goldstandard

Kolloidale Technetium (^{99}Tc) on solide phase
In test meal

Various Protocols
International: (2h), **4h**

Insel add-on
Liquid. 30 min.

Motoric Assessment ?

13C Breath-test

Mixed in Octanic acid (or Spirulina)
in test meal

Exhaled breath at
Every 30 min for 4 hours

Confounding factors, impact by
Small intestinal absorption
SIBO, liver/renal insufficiency

Diagnoses gastroparesis
at higher
rate than scintigraphy (Cave)

Wireless Motility Capsule

Measures pH, temperatur, pressure = detects passage to duodenum

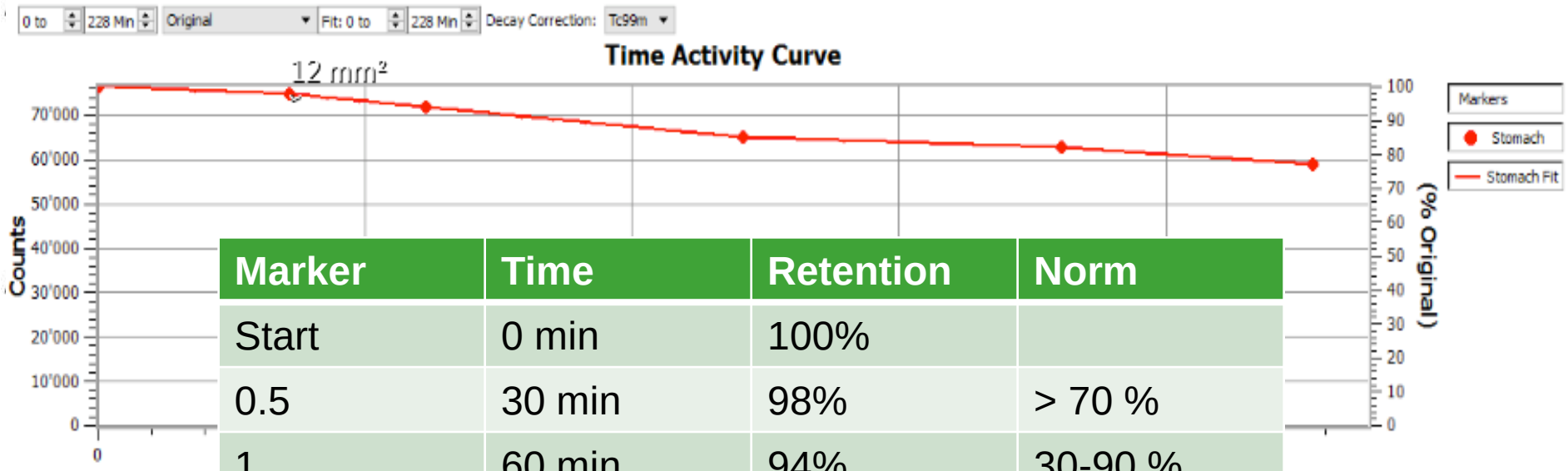
NON-physiological in size
=
non-digestible large object does not exit with the meal

-> **overdiagnosis gastroparesis**

Gastric Emptying Scintigraphy

40 Minutes	40 Minutes	4 hours
		
Liquid = H_2O	**semisolid** = Brei	**solid** = Eiweiss, Toastbrot, Marmelade + 120 ml Wasser

Example: Gastric-Emptying scintigraphy (solid test meal for 4 hours)



Marker	Time	Retention	Norm
Start	0 min	100%	
0.5	30 min	98%	> 70 %
1	60 min	94%	30-90 %
2	121 min	85%	< 60 %
3	180 min	82%	< 30 %
4	240 min	77%	< 10%

Treatment

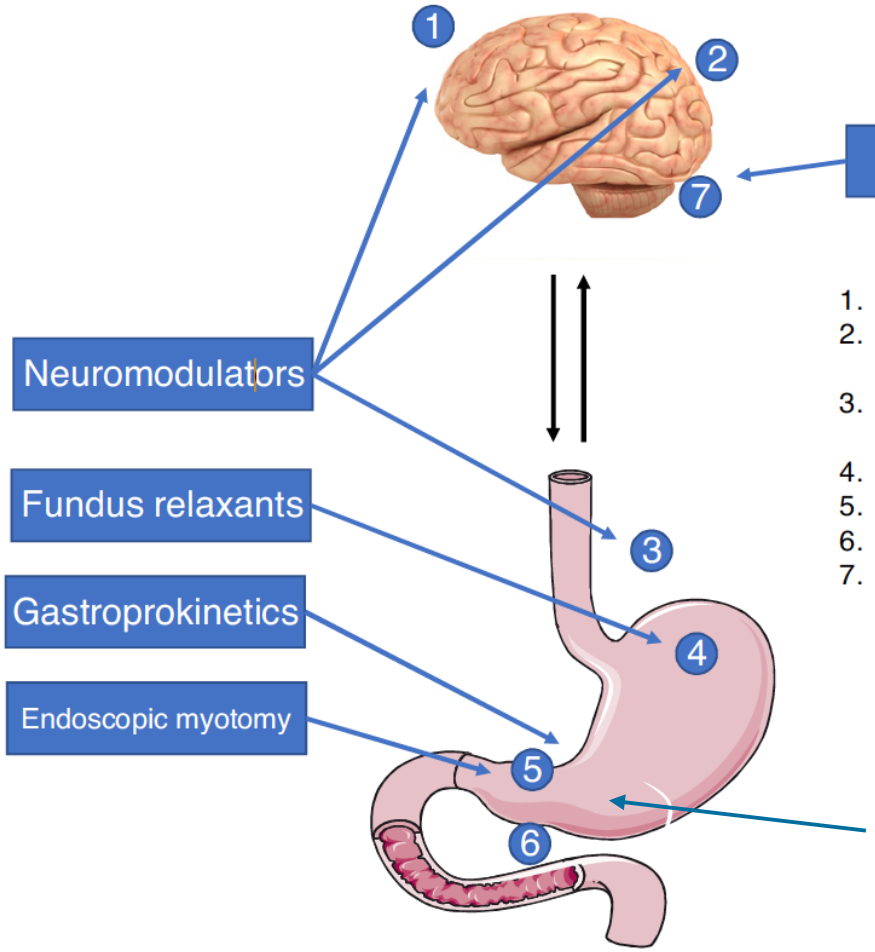
Goals for therapy in Gastroparesis

- **correction of the nutritional state**
- **relief of symptoms (GCSI-Score)**
- **improvement of gastric emptying**

reversal of iatrogenic gastroparesis (chiefly due to opioids)

patients with diabetes: glycemic control

Targets and concepts in treating gastroparesis



1. Anxiety, depression, somatization
2. Central mechanisms of visceral hypersensitivity
3. Peripheral mechanisms of hypersensitivity to gastric distention
4. Impaired gastric accommodation
5. Delayed gastric emptying
6. Low-grade duodenal inflammation
7. Nausea/vomiting center

Pharmacological treatment options in gastroparesis ?

Drug	Mechanism	Adverse effects	Comment
Metoclopramide 10 mg 3-4/day *(Gastrosil, Paspertin, MCP)*	Dopamine D2-receptor-Antagonist 5-HT3-receptor-Antagonist	Dystonic reactions Extrapyramidal symptoms Tardive dyskinesia (< 1%)	The only FDA approved medication for gastroparesis Nasal spray maybe beneficial in women[1] Cave: KI in Parkinson (BBB)
Domperidone 10 mg 3-4/day	Dopamine D2-/3-receptor-Antagonist	Arrythmias Dizziness Light-Headedness	Equal effective like Metoclopramide But less CNS-AE
Erythromycin 250mg 3x/day	Motilin-receptor-Agonist	Abdominal pain, nausea Vomiting	Improves GE Limited/no evidence for long-term use cave: resistance, tachyphylaxis

1: Parkman HP et al. Clin Gastroenterol Hepatol. 2015;13(7):1256–63.e1.

Pharmacological treatment options in gastroparesis ?

Drug	Mechanism	Adverse effects	Comment
Prucalopride* (2-4mg/day)	5-HT4-Agonist	(transient) diarrhoe, headache, abdominal cramps	Standard of care in Insel-SOP RCT-quality data *
Velusetrag[3] (30mg/day)	5-HT4-Agonist	See above	Accelerates GE (> 50% cases > 20%)
Relamorelin	Ghrelin-receptor-Agonist		Phase3-study stopped
Tradipitant[1] Aprepitant[2]	Tachykinin-/ NK1-receptor-Antagonist	Phase 2 data only dizziness, headache	Ameliorates dominantly Nausea (improving GCSI) Approved in Chemotherapy

*: Carbone F et al. AJG 2019
3: Kuo B et al. APT 2021

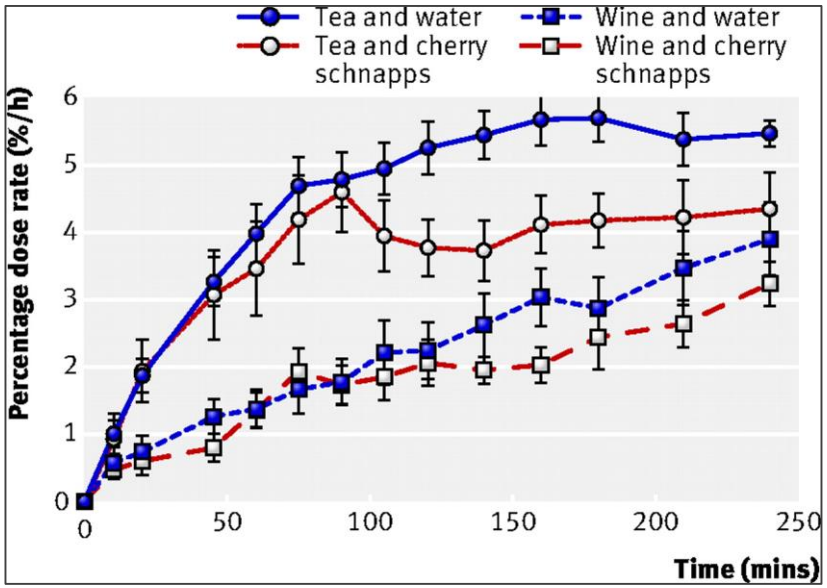
1: Carlin JL et al. Gastroenterology 2021
2. Pasricha PJ et al. Gastroenterology. 2018

Life Style modifications: general recommendations in gastroparesis

What should you drink with cheese fondue: white wine or black tea ? shot schnapps good for digestion ?

Frequent small meals (particle size)
More/Enough liquid
Avoid Fat and Fibre
Increase physical exercise

Glycemic-Control
Avoid noxic agents:
Nikotin, Alcohol



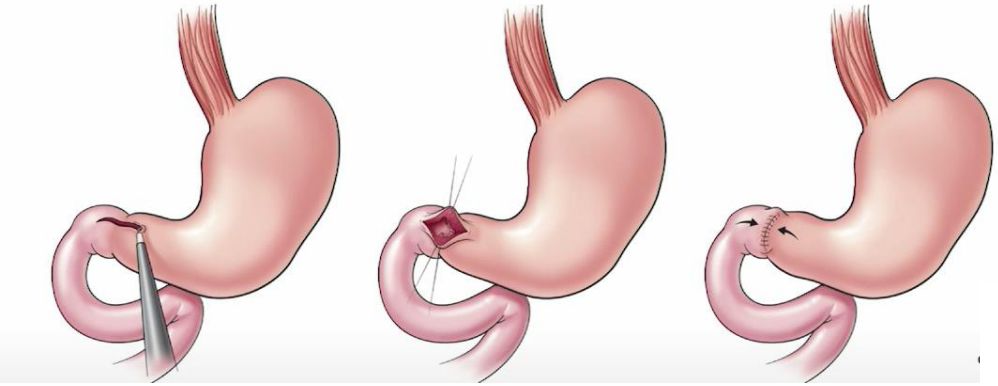
Swiss Fondue and LIquor-Studie
Randomized controlled cross-over

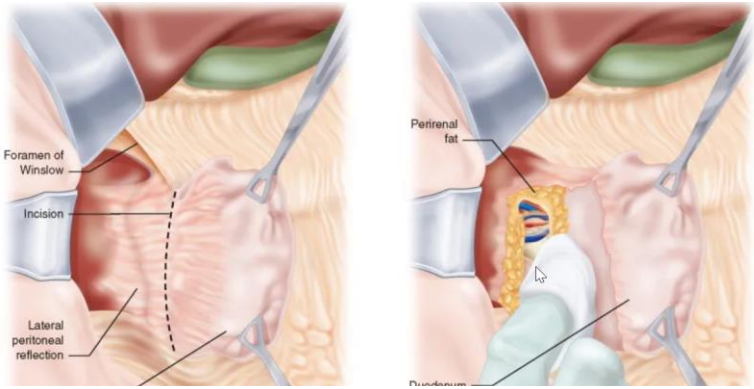
Gastric emptying of swiss fondue: reduced (gastroparesis) and appetit suppressed when
high dose alcohol (wine or liquor)

Paulson EK Radiology 2015 Heinrich BMJ 2010

Life-Style + pharmacological failure → Pyloromyotomy

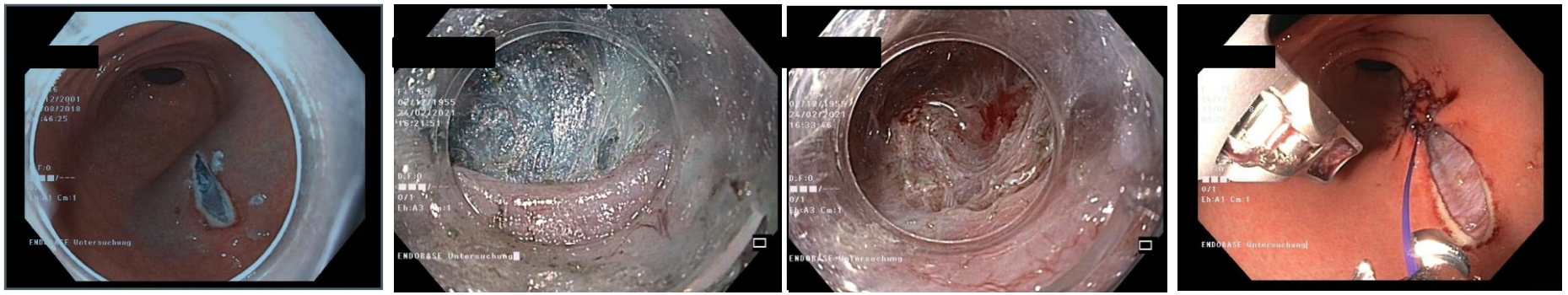
Surgical Heineke-Mikulicz-Pyloroplasty





Traverse inzision along the pylorus
Longitudinal and circular muscle layer cut

Gastric transoral endoscopic pyloromyotomy (G-POEM)



Gastric transoral endoscopic pyloromyotomy (G-POEM)

Meta-analysis (11 studies) 375 patients undergoing G-POEM
Comparator surgical pyloromyotomy (historical) matched analysis
follow-up 6-34 months

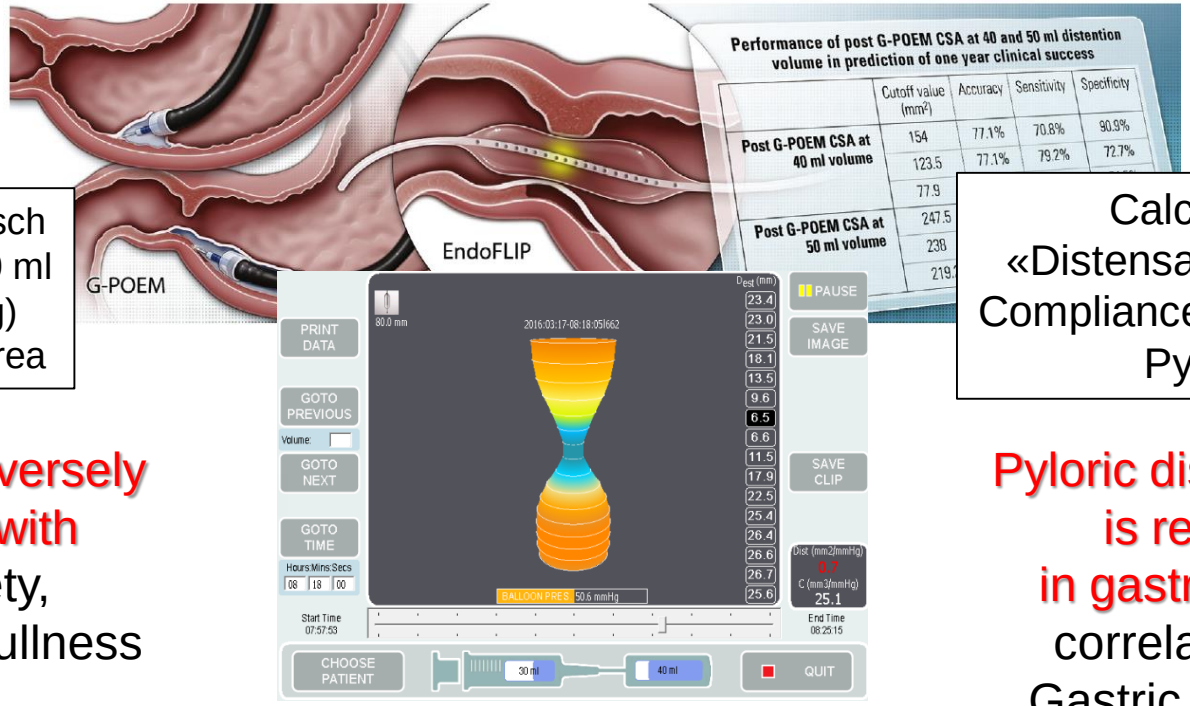
Equally effective to surgical pyloromyotomy
75% clinical success and 84% improved GE

Gastric emptying
(4h scintigraphy) improved
85%

Mohan BP et al. Surg Endoscopy 2020

G-POEM-response and pyloric distensability
Endo-Flip-Compliance-Measurement

Balloon intrapylorisch
Filling to 40 and 50 ml
Pressure (mmHg)
Cross-Sectional-Area



Calculating
«Distensability-Index»
Compliance = Distension
Pylorus

Pyloric CSA inversely correlates with
early satiety,
postprandial fullness

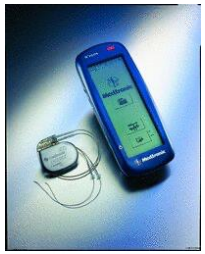
Pyloric distensability is reduced in gastroparesis
correlating with
Gastric emptying

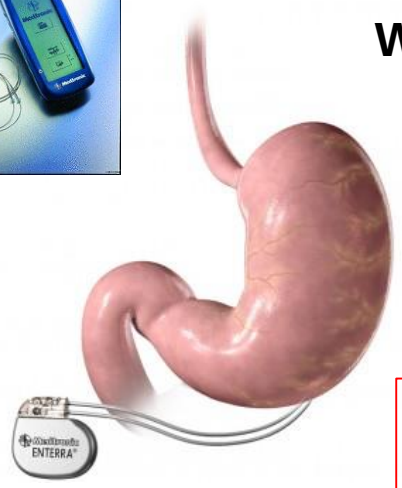
Predictor for clinical success after G-POEM:
area under the curve of 0.83
specificity of 91%, sensitivity of 71%

Malik et al. NGM 2015; Wuestenberghs et al. AJP 2021; Vosoughi et al. Endoscopy 2020

What can Gastric Electric Stimulation help ?

- (over)pacing of slow waves, indirect stimulation
- always combined with pyloromyotomy





mostly uncontrolled studies

WAVESS study: metaanalysis of 13 studies

- Improvement GCSI, **mainly vomiting**, nausea
- decreased need for par/enteral nutrition
- no objective improvement of gastric emptying

Randomized controlled cross-over trial
Focus refractory vomiting in 172 patients (72 diabetic)
Very defined population (> 12 months = chronic disease)

M. Bortolloti et al. Am J Gastro 2002

Durcotte P et al. Gastroenterology 2020

What can Gastric Electric Stimulation help ?

Median-Comparison 2.0 vs. 1.0 p<0.0009

Scoring	Frequency of vomiting
0	Several vomiting episodes a week
1	No more than 1 vomiting episode a week
2	At least 1 vomiting episode a month
3	Less than 1 vomiting episode a month
4	No vomiting episode

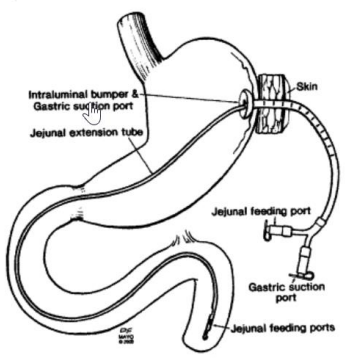
31% min. 1 point Improvement

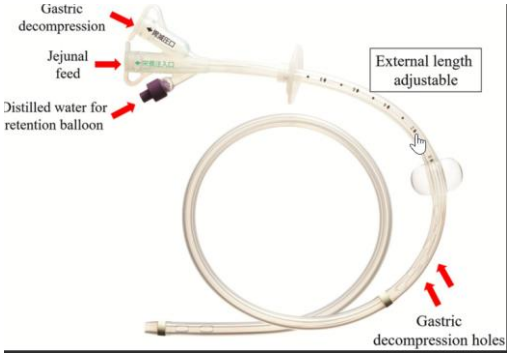
Mode	ITT population (N = 172)	Diabetic Patients (n = 72)	Nondiabetic Patients (n = 100)
ON			
≥1 vomiting episode/mo (score, 0–2)	50.3	44.4	54.7
<1 vomiting episode/mo (score, 3 or 4)	49.7	55.6	45.3
OFF			
≥1 vomiting episode/mo (score, 0–2)	64.4	60.3	67.4
<1 vomiting episode/mo (score, 3 or 4)	35.6	39.7	32.6
	$P = .0006$	$P = .025$	$P = .007$

Durcotte P et al. Gastroenterology 2020

When drugs, POEM, GES fail…… ?

Gastric decompression





Gastric resection = last resort

Roux-Y gastric bypass vs partial (subtotal) gastrectomy

- best results in postsurgical patients
- improvement in >70% of patients
- affects all symptoms (bloating, acid,belching,...) except for pain
- near-total gastrectomy better control of symptoms
  - several studies: st p myotomy, GES, fundoplication
  - assessment of gastroparesis not uniform (liquids vs solids)
- significant weight loss (BMI 32→26kg/m^2)

Bhayani NH. et al. J Gastrointest Surg 2015; 19:411 – 417.
Mancini SA, et al. Am Surg 2015; 81:738 – 746.

Algorythm UVCM Inselspital Bern

Pathologicl GE-Emptying in Scintigraphy
(ideally 4 h solid test-meal plus liquid-test)

⇩

Konservative therapy (mind 6 months):

Life-Style-modification, Glycemic-Control
Pharmacological: Metoclopramide, Domperidone, Resolor

+ (ggf. Antiemesis + ggf. TCA)

⇩

G-POEM/EndoFlip

⇩

Gastral-Electrical-Stimulator

⇩

PEG/J - >> Surgical Ultima-Ratio Resection

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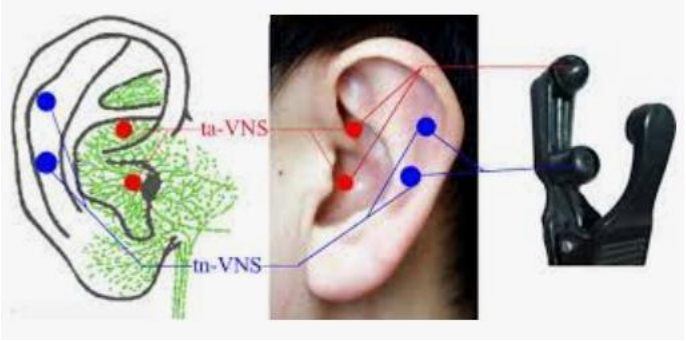
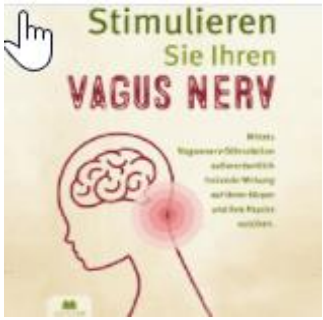
Outlook:
Can you modulate Vagal Nerve activity ?





OPEN LABEL PILOT STUDY: NON-INVASIVE VAGAL NERVE STIMULATION IMPROVES SYMPTOMS AND GASTRIC EMPTYING IN PATIENTS WITH IDIOPATHIC GASTROPARESIS

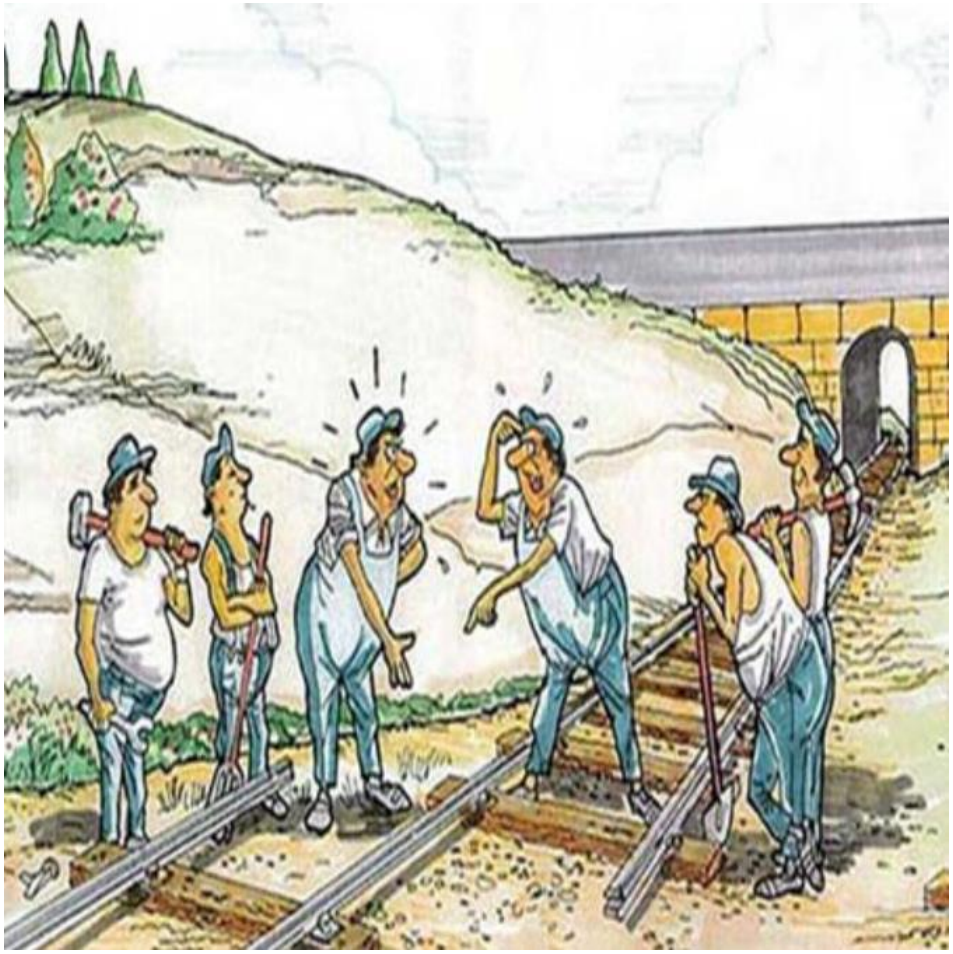
Andres Gottfried-Blackmore, MD PhD*, Emerald P Adler, LMSW, Nielsen Fernandez-Becker, MD-PhD, John Clarke, MD, Aida Habtezion, MD, Linda Nguyen, MD
Division of Gastroenterology & Hepatology, Dept. of Medicine, Stanford University, Stanford, CA, USA.

Neurogastroenterol Motil 2021

4 weeks 2x/day

GE-Scinti T1/2
155→ 129 min

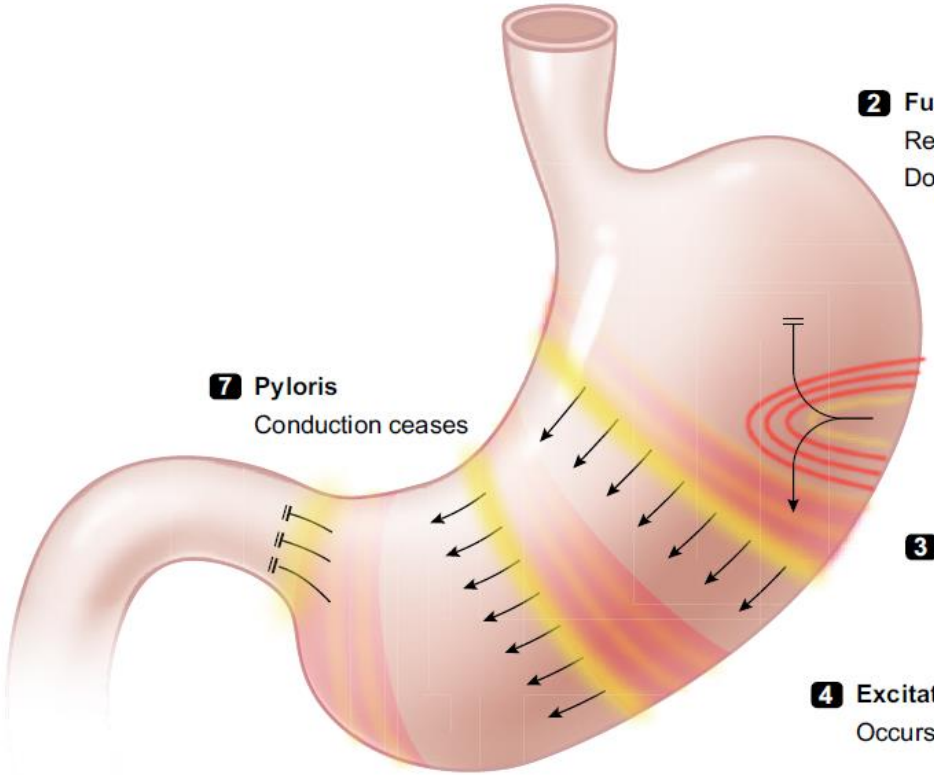
GCSI
2.6→1.8



Thank you
for your
attention

Diagnosing and Managing
Gastroparesis is
Team Work

Gastric Conductance System: Neural Network



2 Fundus
Relatively depolarized.
Does not propagate slow waves.

7 Pyloris
Conduction ceases

1 Pacemaker Region
Initiates regular slow waves at frequencies close to 3 cpm

3 Ring Wavefronts
Rapidly organise due to anisotropic conduction.
Travel antegrade as excitation sleeves at ~3 mm/s

4 Excitation Gap
Occurs between successive wavefronts and wavebacks.

6 Termal Antral Acceleration
Rapid transition to faster velocity (>7 mm/s) ~30 mm from pylorus.
Contributes to the terminal antral contraction.

5 Multiple Propagating Waves
Spaced ~6 cm apart.
Travel faster at greater vs. lesser curvature.

O`Grady G. and Huizinga J Am J Physiol 2021

Peristaltic reflex driving motility and transport of bolus