

**11th Annual Meeting of the GEPD Consortium
&
3rd International Parkinson's Disease
Symposium**

Selected dysautonomic symptoms Diagnosis and treatment

Nico J Diederich
October 8th, 2016

Several systems involved

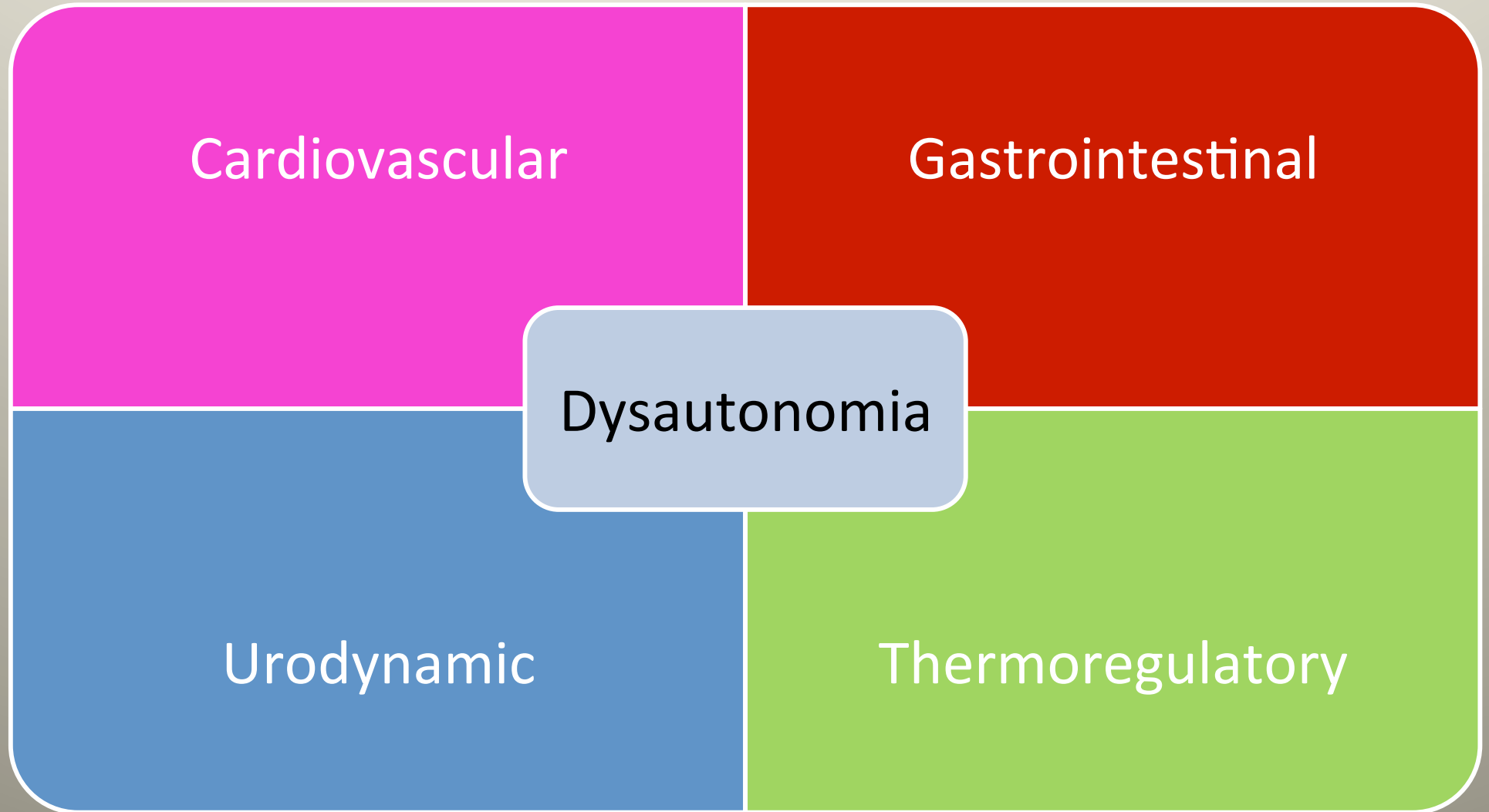
Cardiovascular

Gastrointestinal

Dysautonomia

Urodynamic

Thermoregulatory



Several systems involved

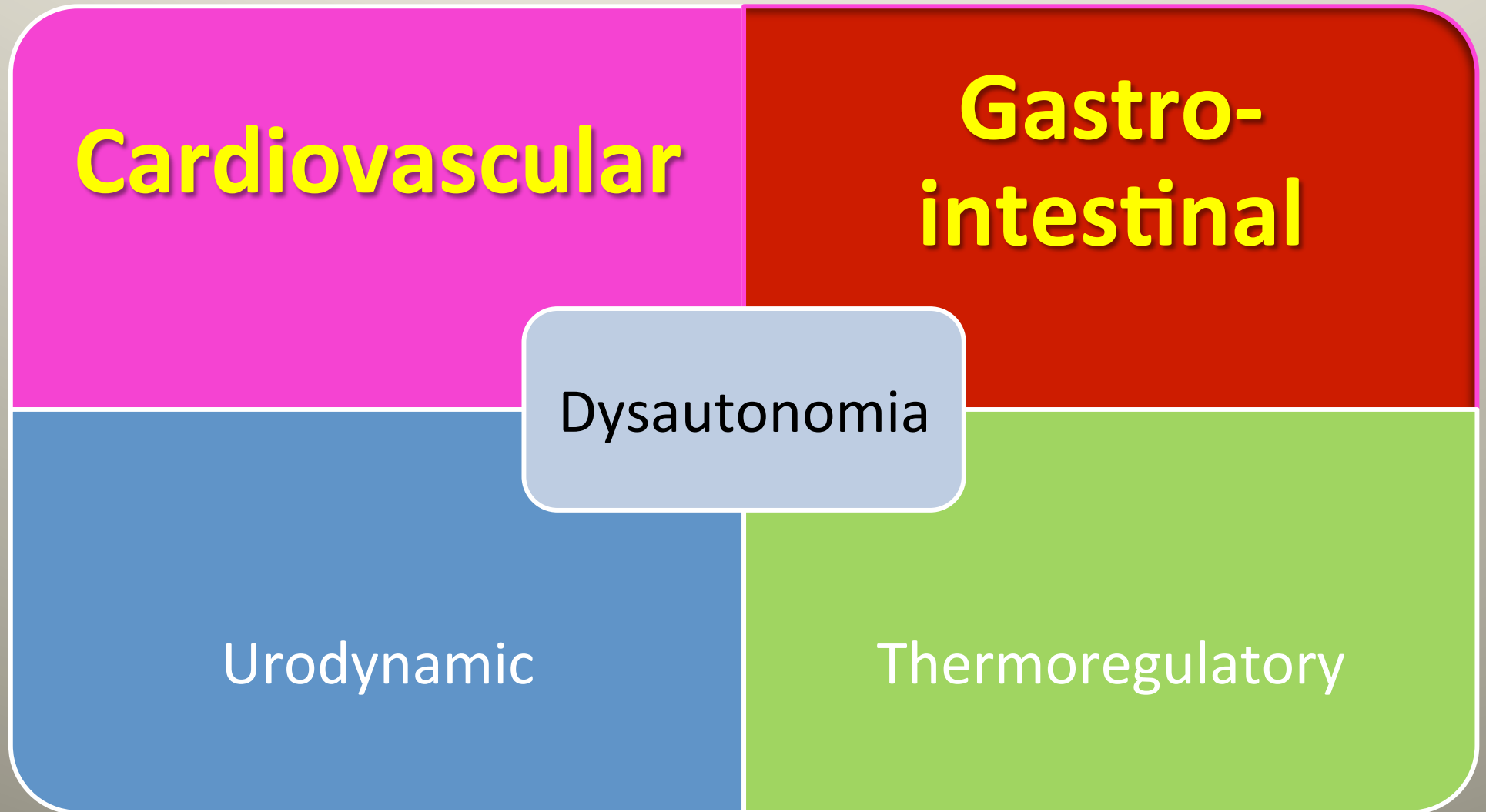
Cardiovascular

**Gastro-
intestinal**

Dysautonomia

Urodynamic

Thermoregulatory



Cardiovascular dysautonomia

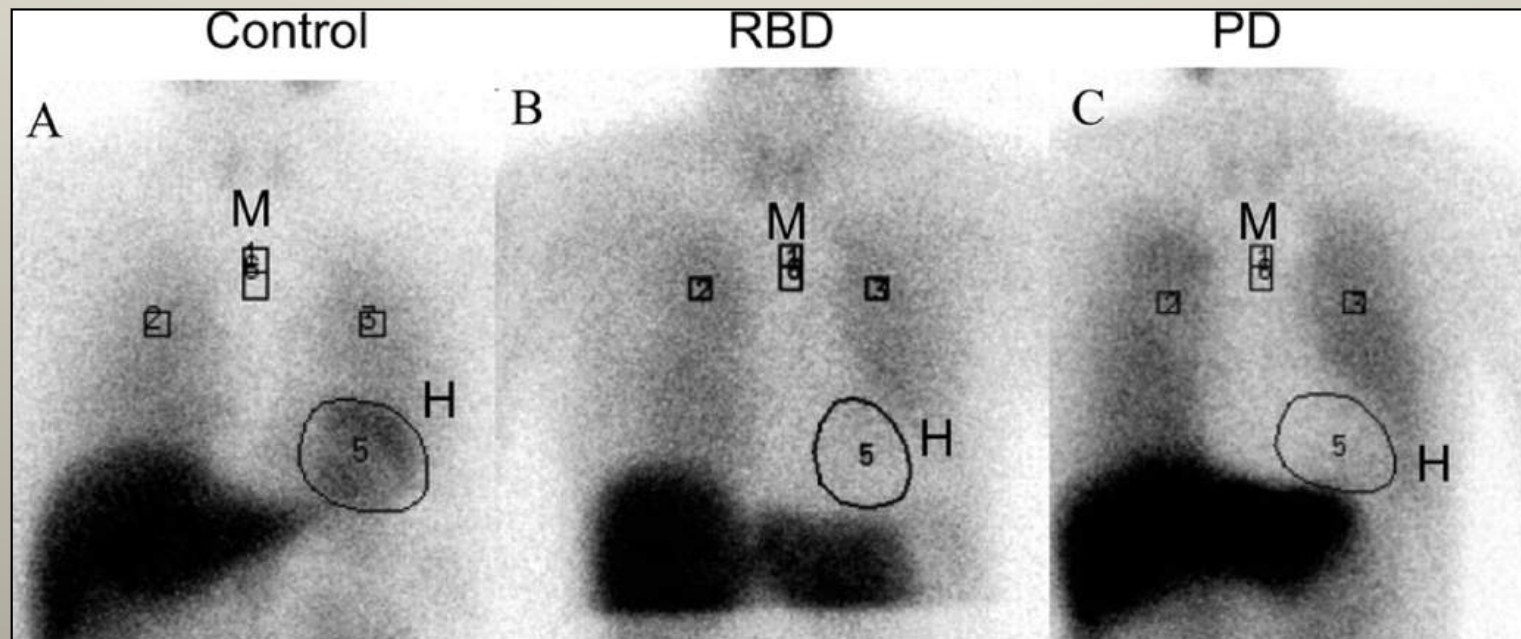
Novelties, therapeutic challenges

...more questions than answers

- MIBG enigma
- Orthostatic hypotension / supine or nocturnal hypertension
- Reduced heart rate variability
- QT and cardiac events

MIBG-SPECT

Reduced postsynaptic noradrenergic uptake



(Miyamoto T, et al., Neurology 2006)

MIBG-SPECT

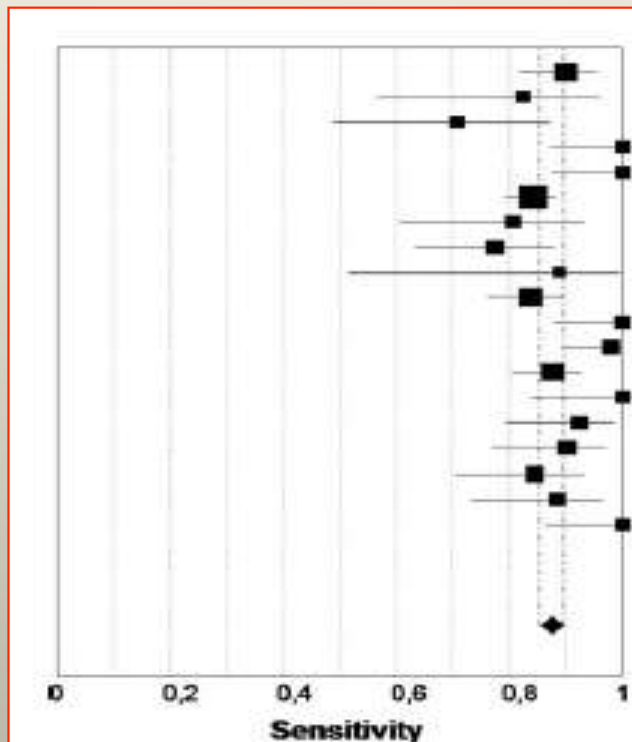
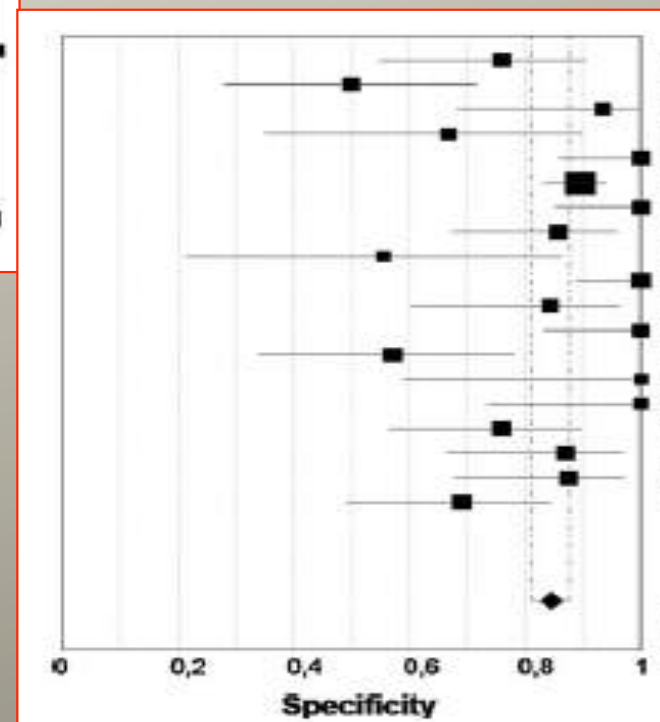
Reduced postsynaptic noradrenergic cardiac uptake

- Beyond any propagation route proposed by Braak et al.
  - Another starting point of disease process?
  - Secondary to Wallerian breakdown?
- PD specific?
- Clinical consequences?
  - No overhooting in phase IV of Valsalva?
  - No acceleration in case of vital danger???

MIBG-SPECT

Meta-analysis

- 1.972 pts, among them 1.076 PD pts.
- Sensitivity for PD 88%
- Specificity for PD 85%
(when discriminating between PD & other Parkinsonism)



*(Treglia G, et al., Clin Auton Res 2012;
Fröhlich I, et al., Neurol Sci 2010)*

MIBG-SPECT

Chronotropic insufficiency as consequence?

FEATURED ARTICLE

Is Cardiac Function Impaired in Premotor Parkinson's Disease? A Retrospective Cohort Study

Jose-Alberto Palma, MD, PhD,^{1*} Maria-Mar Carmona-Abellan, MD,¹ Noelia Barriobero, MD,¹ Cristina Trevino-Peinado, MD,¹ Martin Garcia-Lopez, MD,² Elena Fernandez-Jarne, MD, PhD,² and Maria R. Luquin, MD, PhD^{1*}

¹Department of Neurology, University Clinic of Navarra, Pamplona, Spain

²Department of Cardiology, University Clinic of Navarra, Pamplona, Spain

Movement Disorders, Vol. 28, No. 5, 2013

Cardiac stress test: maximal heart frequency of “only” 143/min :
Prediction of PD after 4 yrs.: sensitivity 83% and specificity 62%

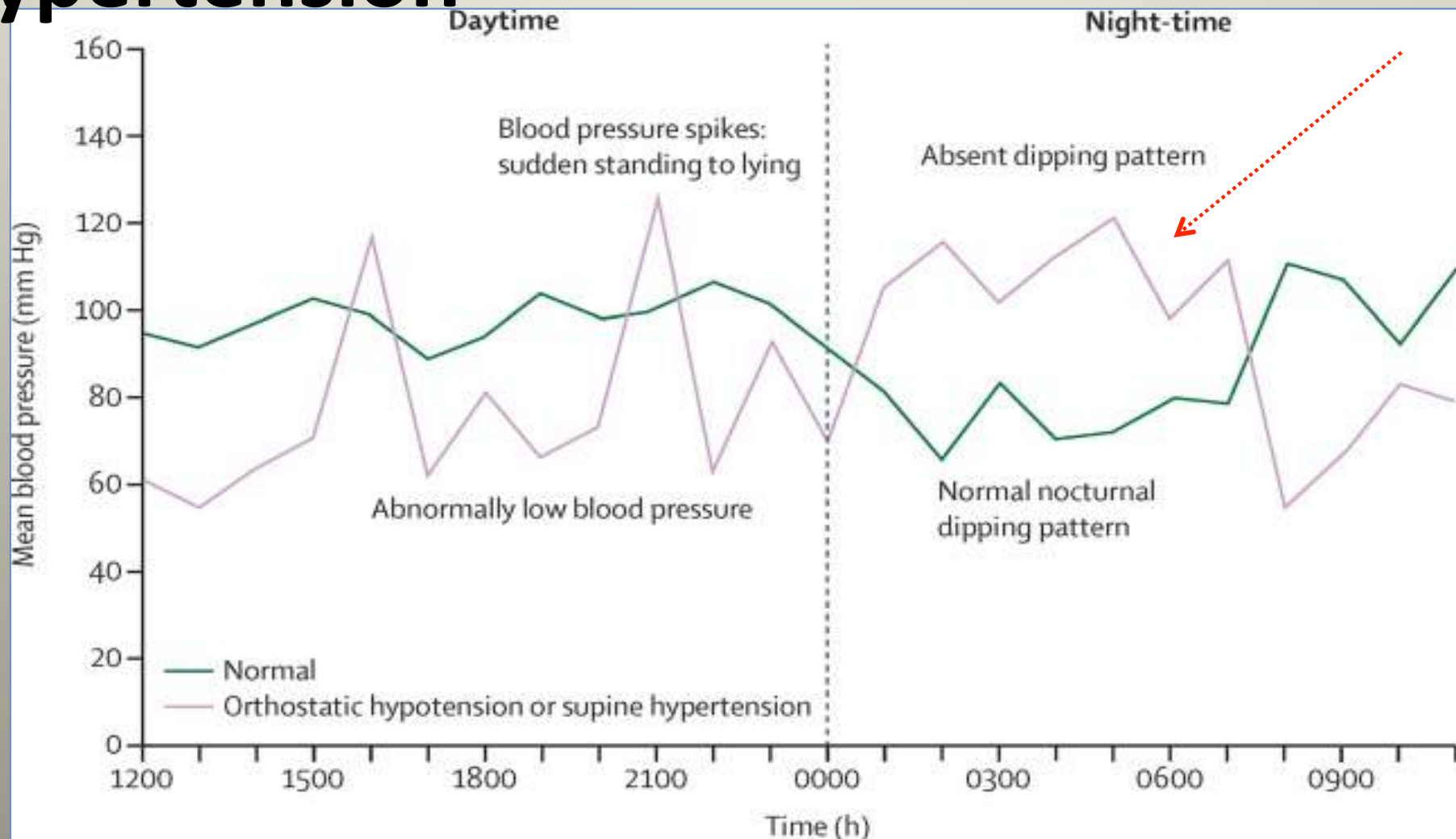
Orthostatic hypotension

- **Def:** Symptomatic BP decrease after arising & standing 3 '
  - systolic ≥ 20 mm HG
  - diastolic ≥ 10 mm HG
- **Pilot study** with 35 PD-pts.
  - 21 (60 %) early OH in premotor phase
- **Five prospective studies** with 24-111 PD pts.
  - 25-50% OH
- **Symptoms:** Dizziness, headache, stiffness of the neck, (pre)-syncope
- No relation with striatal DA-Uptake

(Goldstein, et al., Clin Auton Res 2006; Oh YS, et al., Neurol Sc 2013; Espay AJ, et al., Lancet Neurol 2016)

Paradoxon

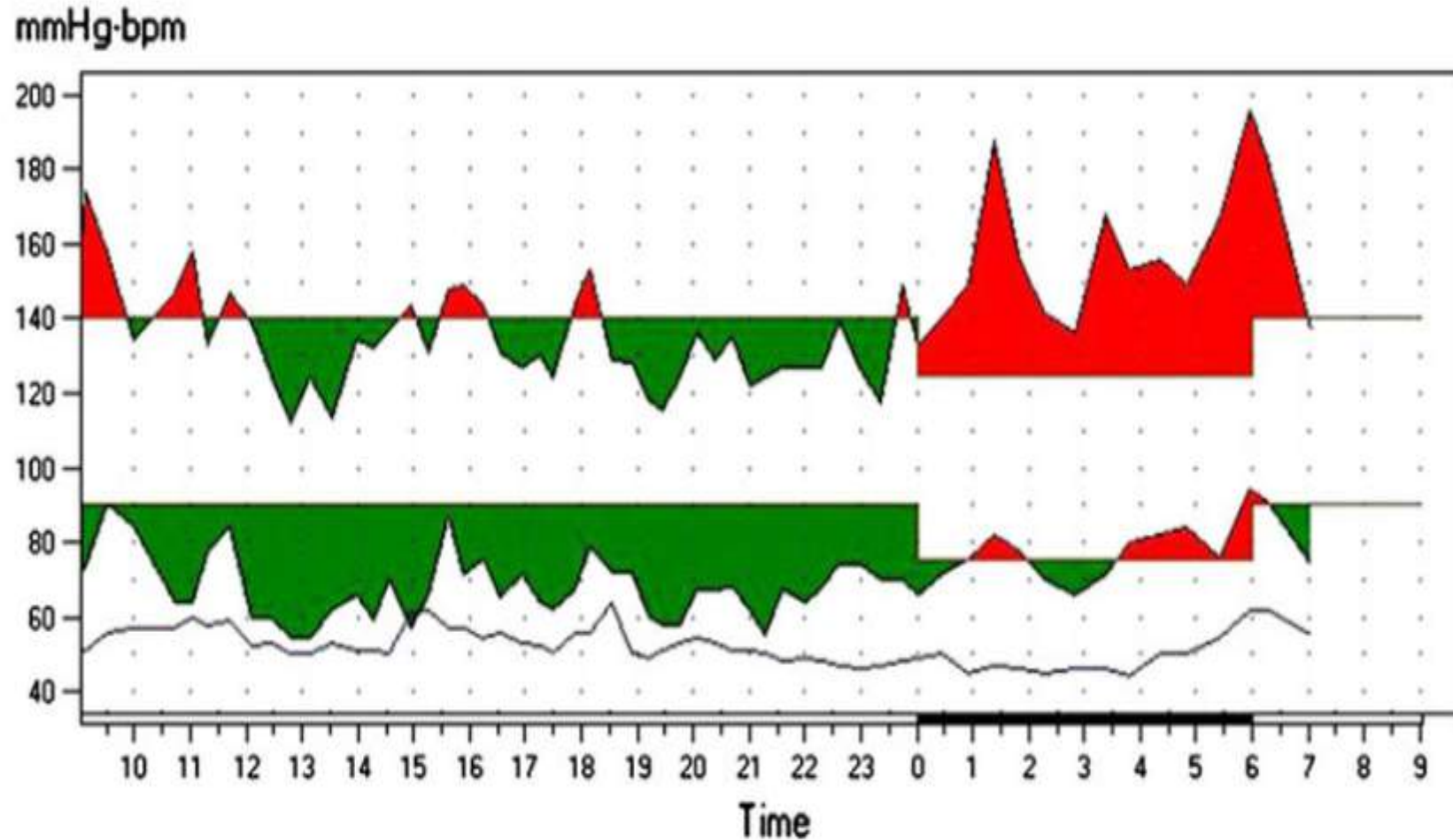
Orthostatic hypotension *and* supine hypertension



(Espay AJ, et al., Lancet Neurol 2016)

Paradoxon

Orthostatic hypotension *and* supine hypertension



(Sharabi Y, et al., J Neurol Sci 2011)

What and when to treat?

Orthostatic hypotension

- Short-term risk for:
- falls
- cognitive impairment
- well explored
- not all patients are symptomatic

Supine hypertension

- Long-term risk for:
- stroke
- myocardial infarction
- extrapolation from general population

(Espay AJ, et al., Lancet Neurol 2016)

What and when to treat?

Orthostatic hypotension

Supine hypertension

UNKNOWN:

- *Is there a safe degree of supine hypertension when treating orthostatic hypotension?*
- *Is nocturnal antihypertensive therapy efficient?*

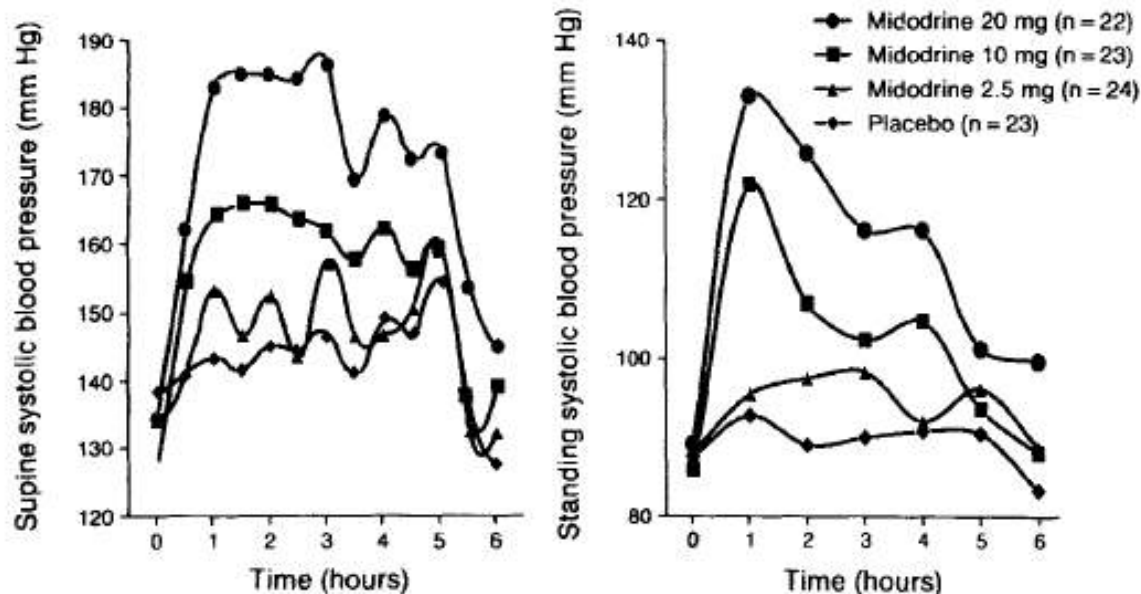
(Espay AJ, et al., Lancet Neurol 2016)

Orthostatic hypotension

Midodrine: alpha 1-Agonist

A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension

R.A. Wright, MB ChB, MD, FRACP; H.C. Kaufmann, MD; R. Perera, MB BS, MRCP; T.L. Opfer-Gehrking; M.A. McElligott, PhD; K.N. Sheng, PhD; and P.A. Low, MD



Dose-dependent effect

(Neurology 1998)

Orthostatic hypotension

no evidence-based therapy

Efficacy

Orthostatic hypotension

Fludrocortisone	Insufficient evidence
Domperidone	Insufficient evidence
Midodrin	Insufficient evidence
Dihydroergotamine	Insufficient evidence
Etilefrine hydrochloride	Insufficient evidence
Indomethacine	Insufficient evidence
Yohimbine	Insufficient evidence
L-threo-3.4-dihydroxyphenylserine	Insufficient evidence

Orthostatic hypotension

expert opinion

Neurogenic orthostatic hypotension

Lifestyle

- Increase water and salt intake
- Stand up slowly
- If possible, perform exercises (eg, leg crossing, squatting) to reduce lower body blood pooling
- Avoid alcohol
- Avoid autonomic stressors (eg, long exposure to hot water)
- Consider thigh-high compression stockings with or without abdominal binder
- Sleep with head of the bed elevated by 15–23 cm

Adjustment of pharmacotherapy

- Whenever possible, replace fludrocortisone with a short-acting pressor (eg, midodrine, droxidopa)
- When possible, the patient should use pressor agents as required
- Use the lowest dose of pressor agent that controls symptoms
- Consider treating postprandial hypotension with acarbose (an α -glucosidase inhibitor that decreases intestinal glucose absorption)
- Consider treating mild disease with pyridostigmine
- Assess all drugs for unwanted, avoidable cardiovascular effects

Supine hypertension

expert opinion

Supine hypertension

Lifestyle

- Avoid the supine position during the day, especially after taking a pressor agent
- Have a snack before bedtime (to induce postprandial hypotension)
- Sleep with head of the bed elevated by 15–23 cm

Adjustment of pharmacotherapy

- If antihypertensives are needed, avoid α -blockers and diuretics
- Assess all medications for unwanted, avoidable cardiovascular effects
- Consider bedtime therapies, such as transdermal nitroglycerin patches, the phosphodiesterase-5 inhibitor sildenafil, the β -blocker nebivolol, the angiotensin-receptor antagonist losartan, or the vasodilators hydralazine or minoxidil
- In multiple system atrophy (in which residual sympathetic tone can increase supine hypertension), the sympatholytic agent clonidine can be useful

Reduced heart rate variability

RESEARCH ARTICLE

Reduced Sympathetically Driven Heart Rate Variability During Sleep in Parkinson's Disease: A Case-Control Polysomnography-Based Study

Nicolas Sauvageot, M. STAT¹, Michel Vaillant, PHD¹, Nico J. Diederich, MD^{2*}

¹Centre de Recherche Publique Santé, Centre d'Etudes en Santé, Strassen, Luxembourg

²Department of Neurosciences and Interdisciplinary Sleep Laboratory, Centre Hospitalier de Luxembourg, Luxembourg-City, Luxembourg

REM SLEEP BEHAVIOR DISORDER

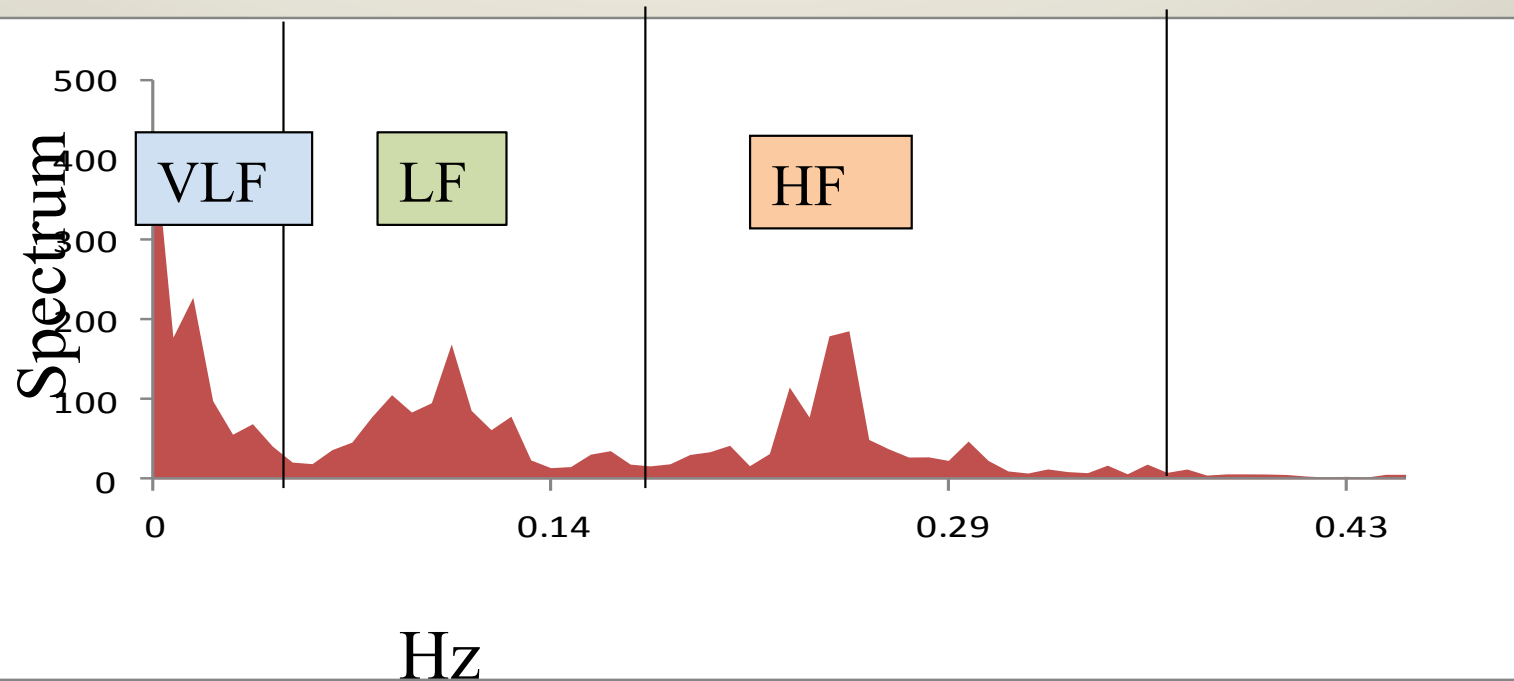
Cardiac Autonomic Regulation During Sleep in Idiopathic REM Sleep Behavior Disorder

Paola A. Lanfranchi, MD, MSc^{1,2}; Lorraine Fradette, BS²; Jean-François Gagnon, PhD²; Roberto Colombo, BEng³; Jacques Montplaisir, MD, PhD²

¹Department of Medicine, Cardiology Division, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada; ²Centre d'étude du sommeil et des rythmes biologiques, Hôpital du Sacré-Coeur de Montréal, Montréal, Canada; ³Bioengineering Department, Salvatore Maugeri Foundation, Veruno, Italy

(Mov Disord 2011; Sleep 2010)

Analysis of frequency domain



VLF : Ultra Low Frequency : 0.003-0.04 Hz

LF : Low frequency, mainly **sympathetic** influences :
0.04-0.15 Hz

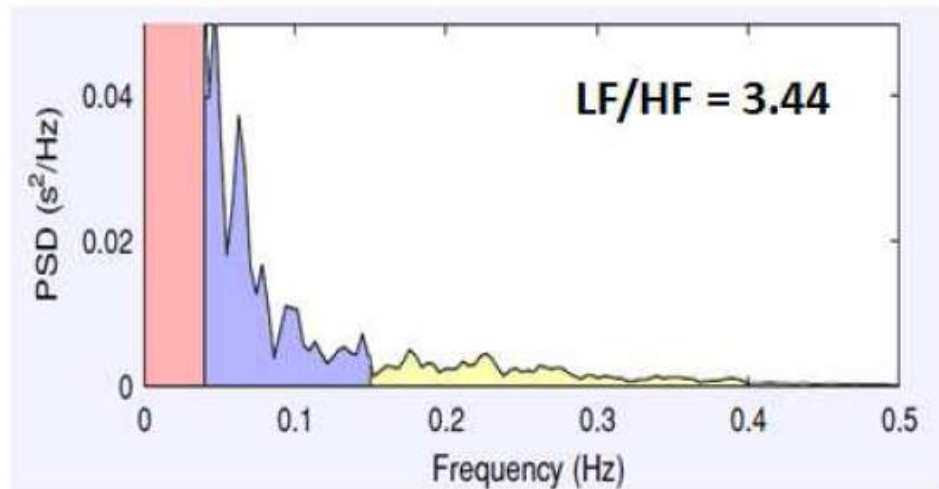
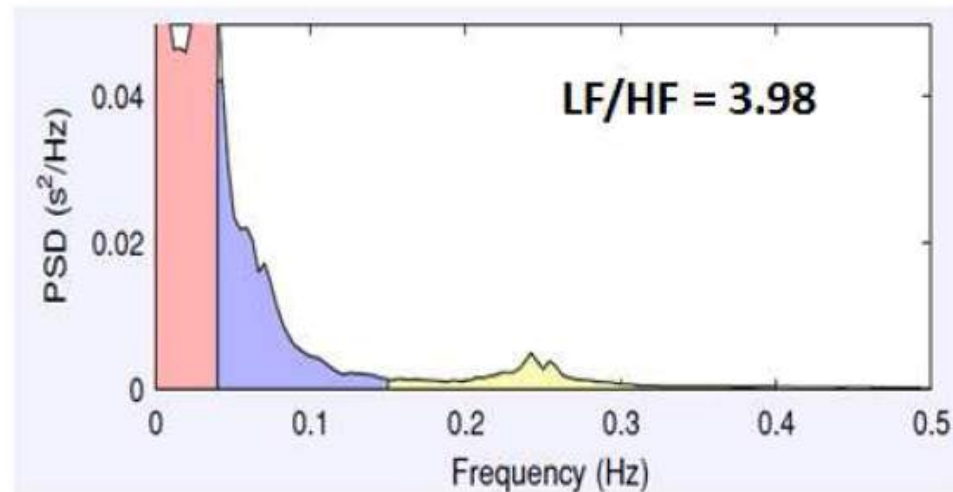
HF : High frequency, mainly **parasympathetic** influences :
0.15-0.40 Hz

Figure 2

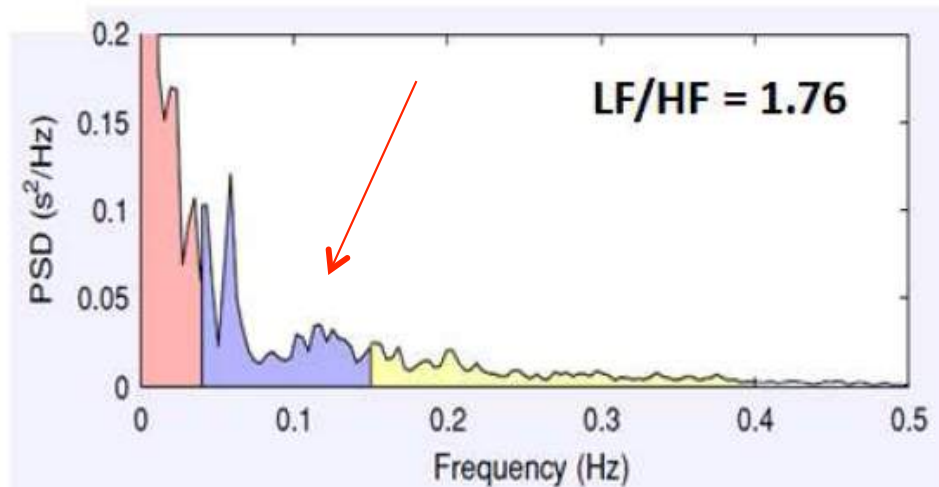
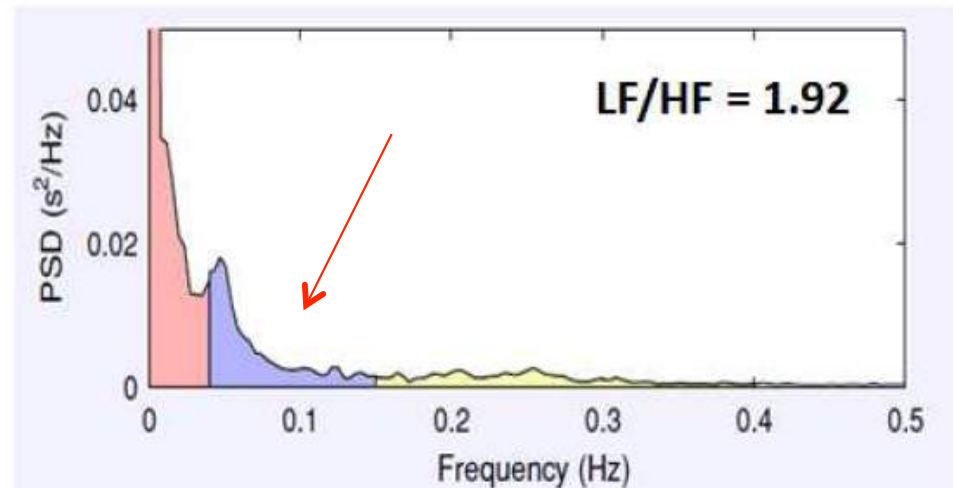
REM

NREM

Control #42



IPD patient #11



Reduced heart rate variability

- Concerns mostly, but not exclusively **sympathetic** influence (reduced)
- PD pts.: daytime, NREM sleep, REM sleep
- RBD pts.
- Cause(s)?
  - Postganglionic noradrenergic denervation
  - Central and peripheral noradrenaline deficiency (locus coeruleus, sympathetic ganglia)
  - Vagal dysfunction
- No data on secondary cardiac (dys)function

Prolongation of QT-Interval

disease effect

- PD pts.: 418 +/- 14 ms
Controls: 403 +/- 18 ms
- No relationship with levodopa treatment
- Pts. Hoehn & Yahr II: 410 +/- 12 ms
- Pts. Hoehn & Yahr III: 424 +/- 12 ms

(Oka et al, Eur Neurol 1997)

Prolongation of QT-Interval

medication effect

- 506 PD pts.; disease duration 11.2 ± 6.5 yrs.
- Medications with potential QT prolongation
  - citalopram, escitalopram, venlafaxine, sertraline, domperidone, amantadine, solifenacin
- **Cardiac events in 24 patients (4.7%)**
  - 15 dysautonomia
  - 4 history of heart disease
  - 8 one or more drugs with a potential cardiac adverse effect
- Triggering effect significant for: age, disease duration, dysautonomia, PD dementia ($p < 0.05$)

(Heranval A, et al., Rev Neurol 2016)

Domperidone & cardiac events

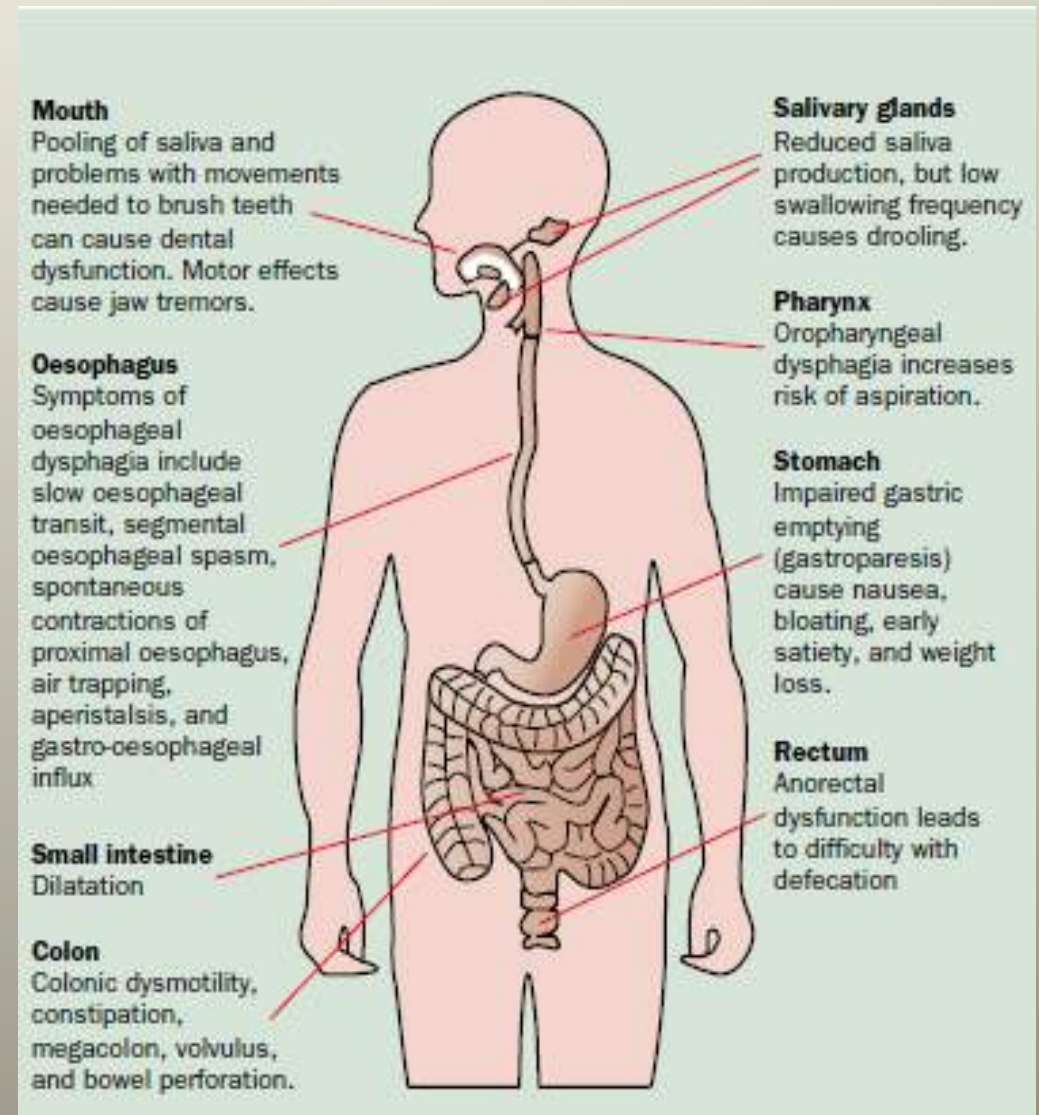
- Ventricular tachyarrhythmia and sudden cardiac death with domperidone use in Parkinson's disease.
- 214.962 PD pts. & 886 581 person-years
- 2907 cases of VT/SCD
- 22% increase with domperidone; risk = *non* significant
- Pre-existing cardiovascular disease; risk = significant (RR 1.38)

(Renoux C, et al., Br J Clin Pharmacol, 2016)

Gastrointestinal dysautonomia

- **Why and when involvement?**
- **Dysphagia**
- **Constipation**
  - Risk factor
  - Different types
  - Treatment

Again more questions than answers



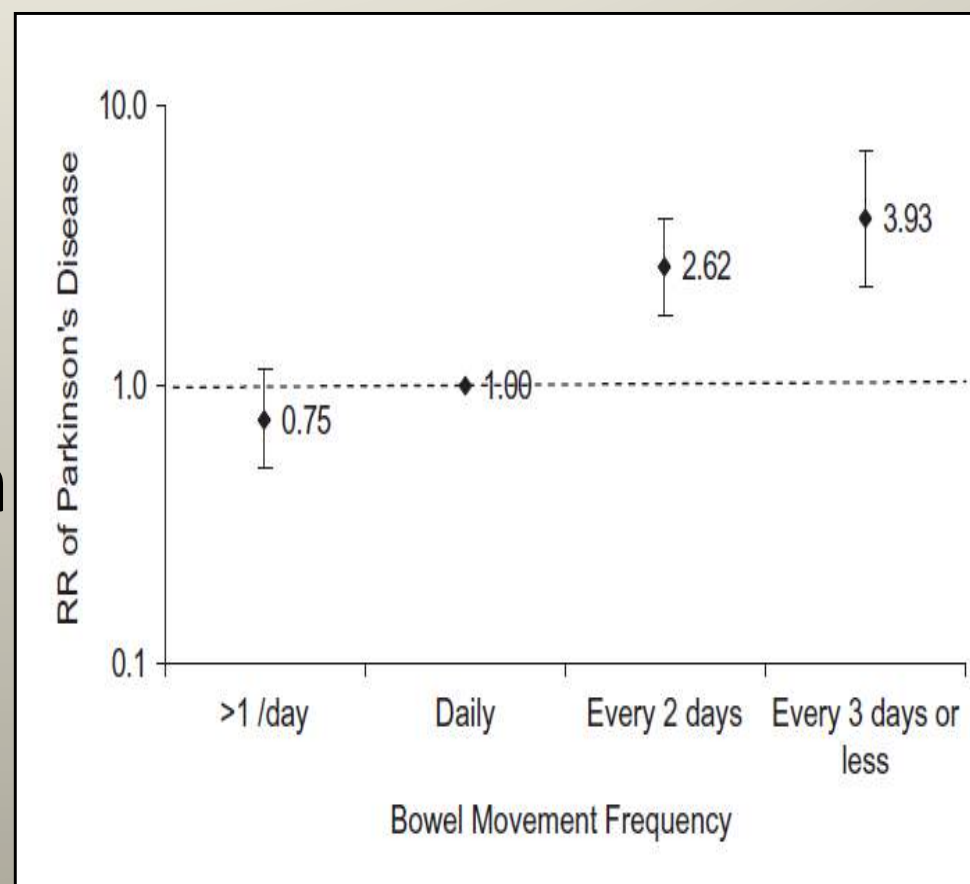
Constipation: risk factor for PD?

Honolulu Heart Study

> 6,000 men between
51- 75 yrs.

risk for later PD:

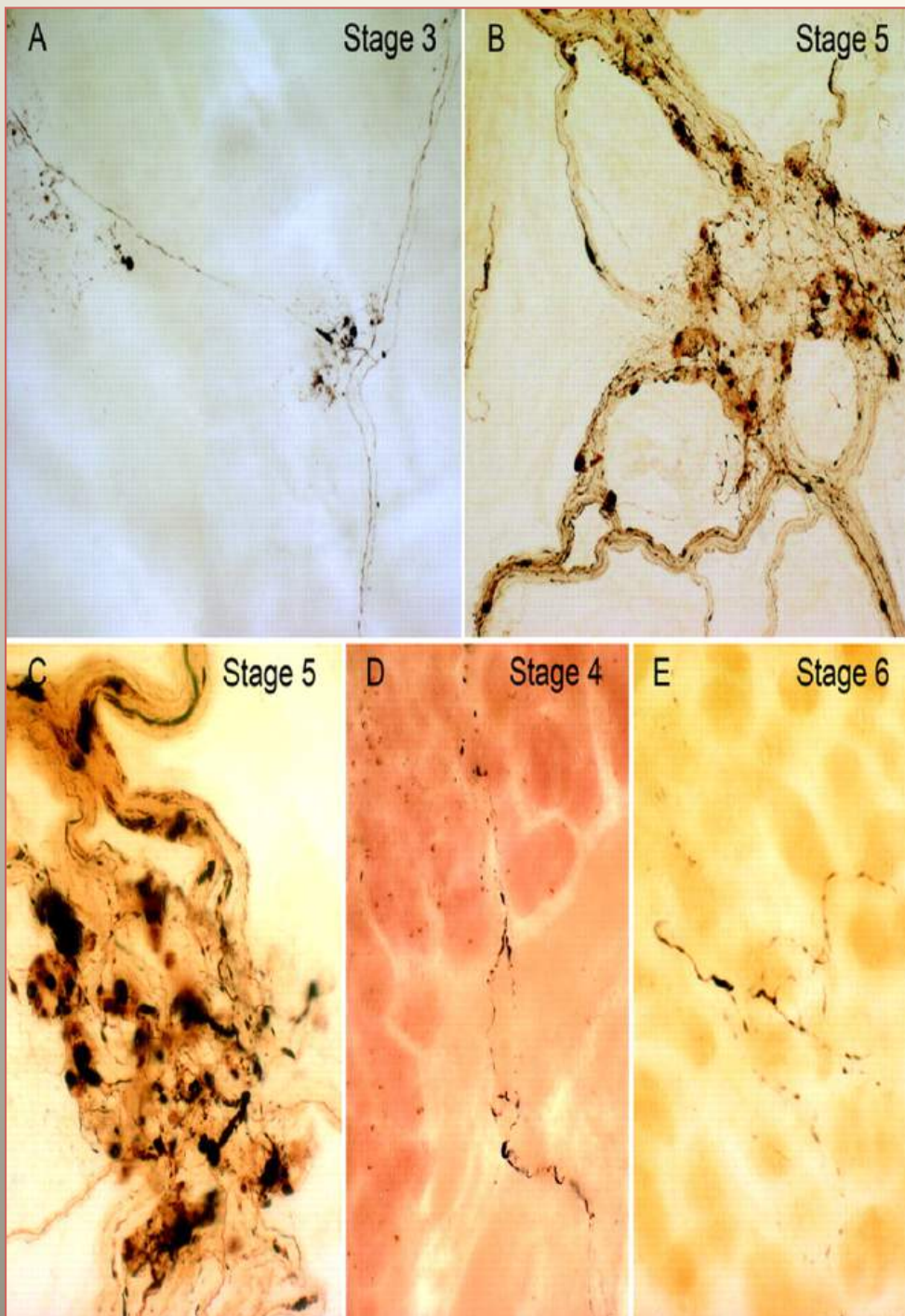
$\geq 4X$ increased in men
with < 1 stool/d



Abbott RD, et al., Neurology 2001 and Mov Disord 2007; Gao X, et al., Am J Epidemiol 2011)

Braak's postulate: Enteric nervous system: = entry point

retrograde axonal
transport of
« pathogenic agent »
to motor nucleus of
vagal nerve?

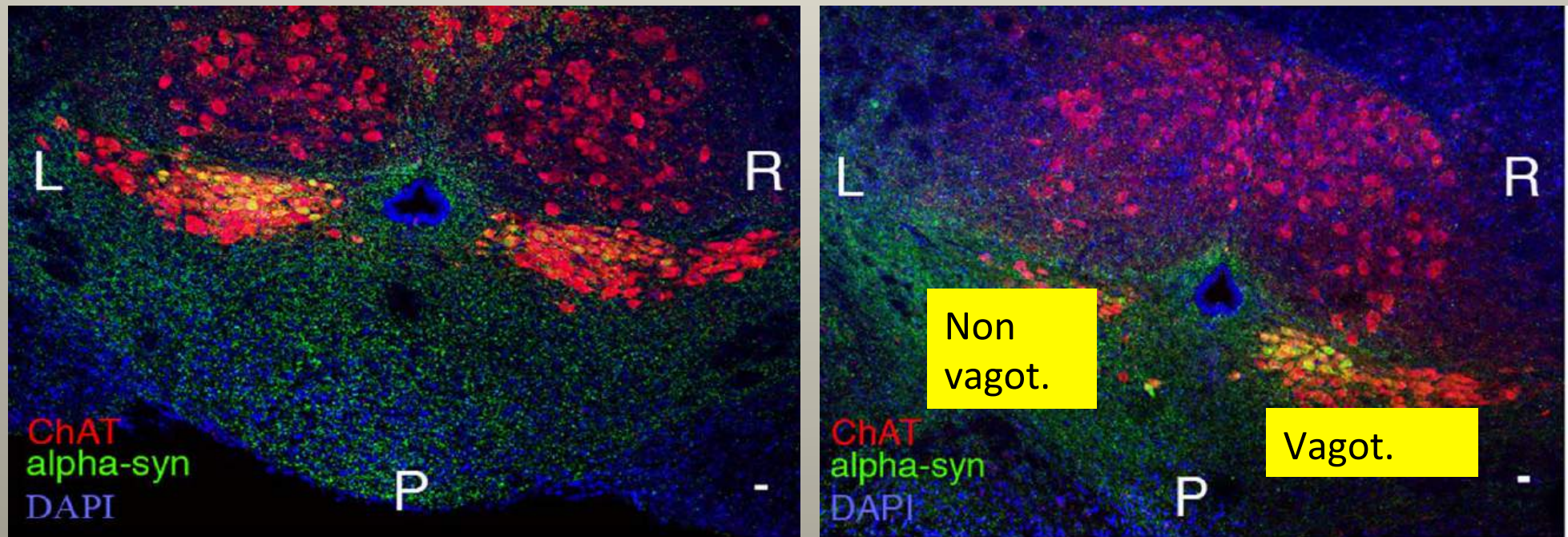


(Braak H, del Tredici K, Neurology 2008)

Vagotomy...protective against PD?

mice

- Hemivagotomy prevents α -synuclein accumulation in the ipsilateral dorsal motor vagus (DMV)

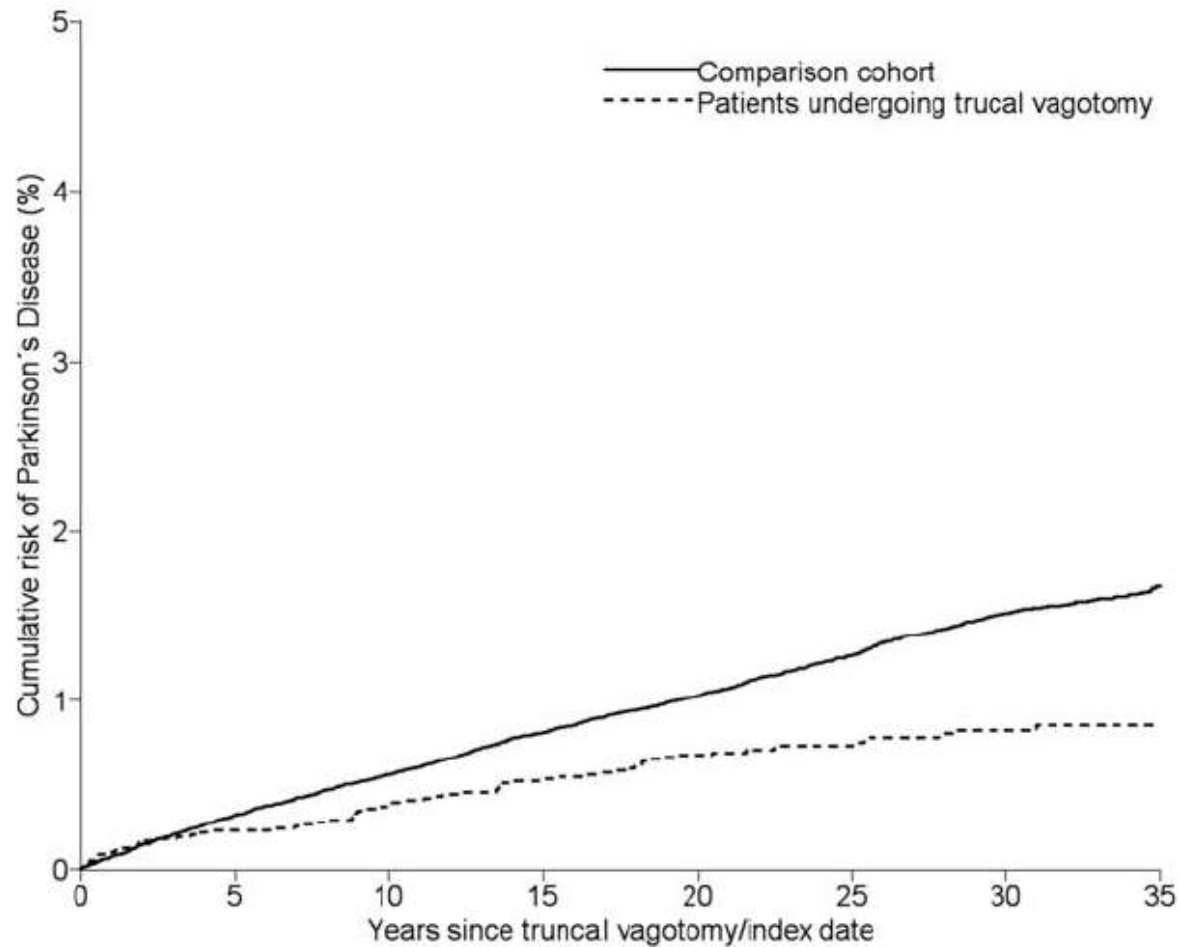


After gastric exposure to rotenone, a potent environmental toxin

(Pan-Montojo F, et al., Sci Rep 2012)

Vagotomy...protective against PD?

humans



Yes, when truncal
(both vagal trunks)

No, when
superselective (only
nerves supplying
fundus and body of
the stomach)

Road closed: what does it mean?



- Other propagation routes?
- Entry point:
stomach, colon
or ...appendix?
(Appendectomy protective =
not proven)
- To look at the colon?

- Cutting the vagal highway blocks one point of entry for prion-like alpha-synuclein

(Kaufmann H, Ann Neurol 2015;)Marras C, et al., Mov Disord 2016; Mendes A, et al., Mov Disord 2015; Svensson E, et al., Mov Disord 2016)

Colon as entry point : a two-part saga

1. Submucosa

RESEARCH ARTICLE

Alpha-Synuclein in Colonic Submucosa in Early Untreated Parkinson's Disease

Kathleen M. Shannon, MD,^{1*} Ali Keshavarzian, MD,² Ece Mutlu, MD,² Hemraj B. Dodiya, MS,³ Delia Daian,² Jean A. Jaglin, RN,¹ and Jeffrey H. Kordower, PhD³

¹Departments of Neurological Sciences, Rush Medical College, Chicago, Illinois, USA

²Department of Gastroenterology and Nutrition, Rush Medical College, Chicago, Illinois, USA

³Center for Brain Repair, Rush Medical College, Chicago, Illinois, USA

✓ already present in presymptomatic cases

(Shannon KM , et al., Mov Disord 2012a and b; Forsyth CB, et al., PLoS One 2011; Kelly LB, et al., Mov Disord 2014)

Colon as entry point : a two-part saga

1. Submucosa

OPEN ACCESS Freely available online



Colonic Biopsies to Assess the Neuropathology of Parkinson's Disease and Its Relationship with Symptoms

Thibaud Lebouvier^{1,2,3,4,*}, Michel Neunlist^{1,4,6,*}, Stanislas Bruley des Varannes^{1,2,3,6}, Emmanuel Coron^{1,2,3,6}, Anne Drouard², Jean-Michel N'Guyen⁷, Tanguy Chaumette^{1,4}, Maddalena Tasselli^{1,4}, Sébastien Paillusson^{1,4}, Mathurin Flamand^{1,2,3,6}, Jean-Paul Galmiche^{1,2,3,6}, Philippe Damier^{2,3,5}, Pascal Derkinderen^{1,2,3,5,6,*}

¹ UMR 913, Inserm, Nantes, France, ² CIC-04, In: Nantes, Nantes, France, ⁵ Service de Neurologie, CHU d'Information Médicale, Évaluation et Santé Publique

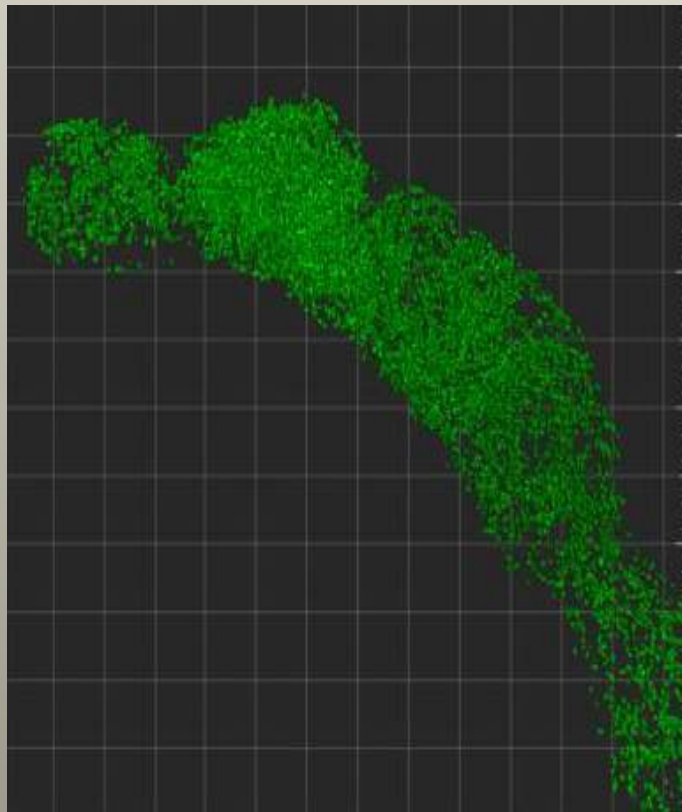
Analysis of the ENS by routine colonoscopy biopsies is a useful tool for pre-mortem neuropathological diagnosis of PD

Université de France, ⁷ Pôle

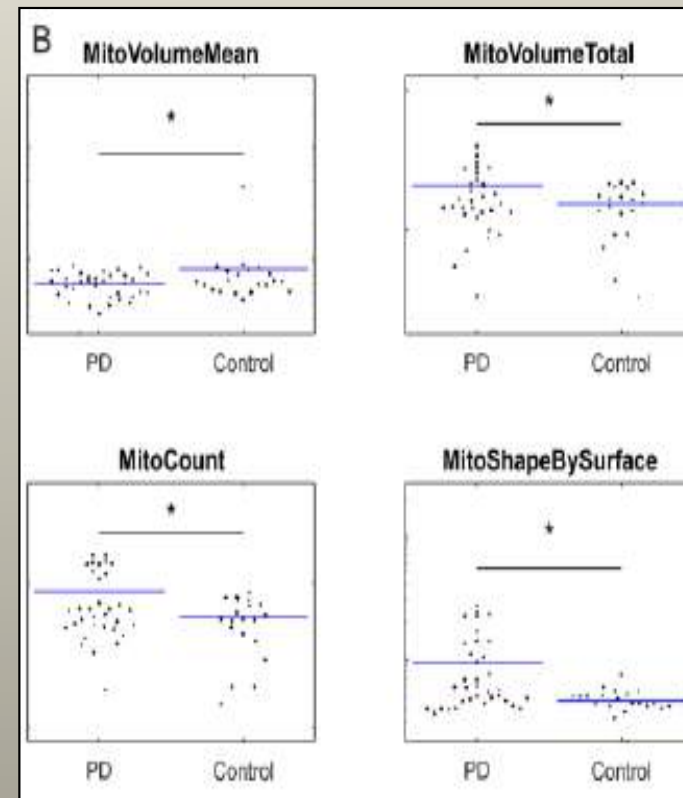
Colon as entry point : a two-part saga

1. Submucosa

Ex vivo study on mitochondria in enteric neurons of PD pts. at early stage



Mitochondria count in ganglion



Changes in numbers and volume in left colon

(Baumuratov A, Antony P, et al., Sci Rep 2016)

Colon as entry point : a two-part saga

1. Submucosa

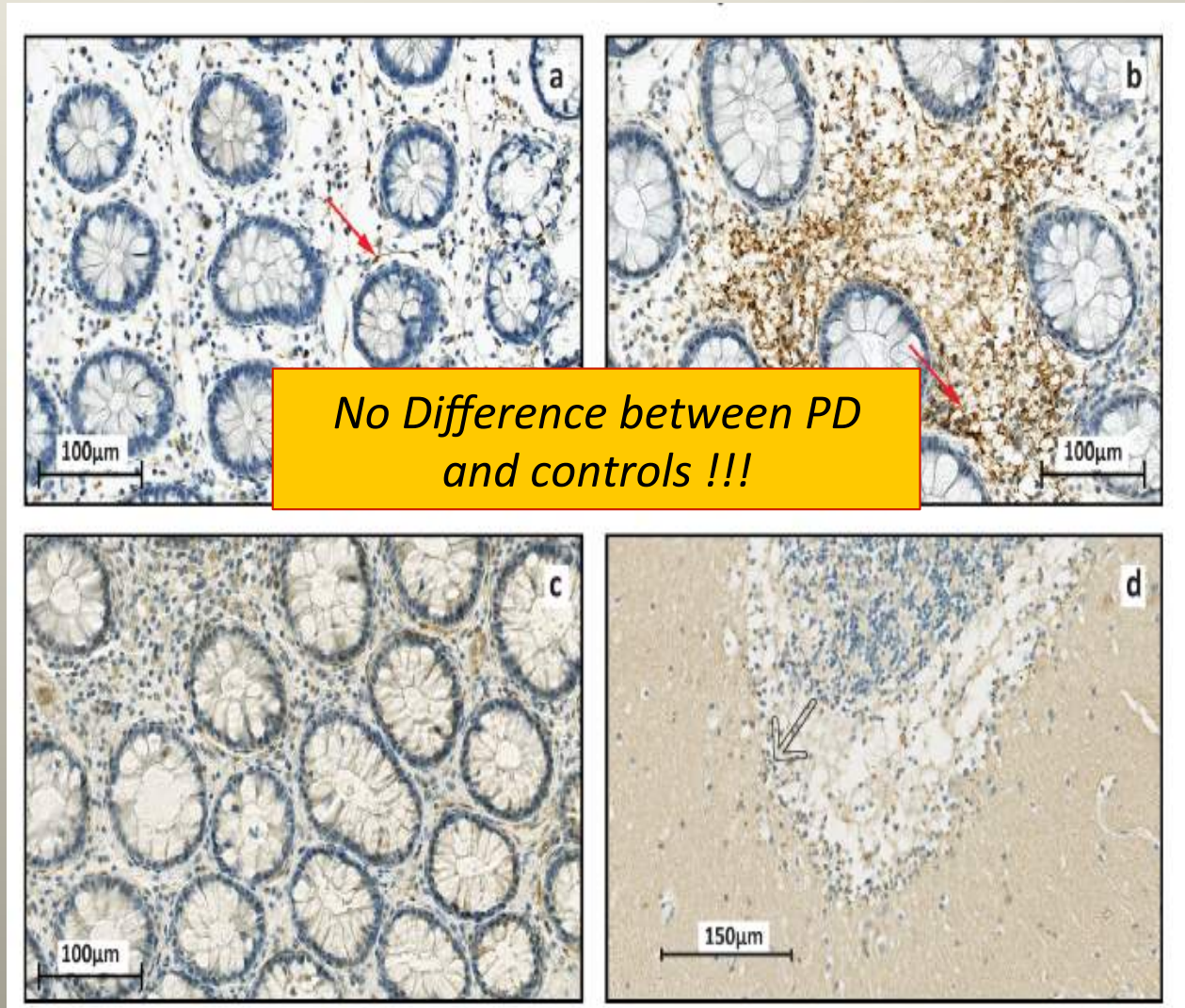
Morphometric mitochondrial changes in enteric neurons

- **In left colon:** increase in mitochondrial mass, but yet unchanged ganglia volumes
→ mitochondrial compensation?
- **In right colon:** reduced ganglia volumes
→ mitochondrial compensation already failed?

Colon as entry point : a two-part saga

2. Mucosa

- Different cohorts
- Different staining methods
- Separation
  - total α syn
  - phosphorylated α syn
- Discussion
  - Posttranslational modifications of α syn inducing PD?
  - Transitory phenomenon («Tornado»)?



(Visanji NP, et al., Neurology 2015; Xiang W, et al., Mol Neurodegener 2015; Chung SJ, et al., Mov Disord 2016; Antunes L, et al., Mov Disord 2016)

Constipation

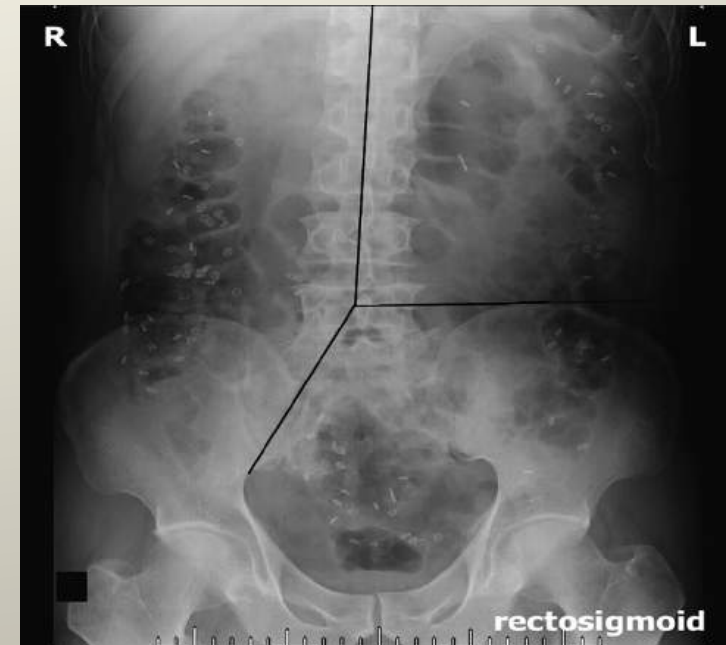
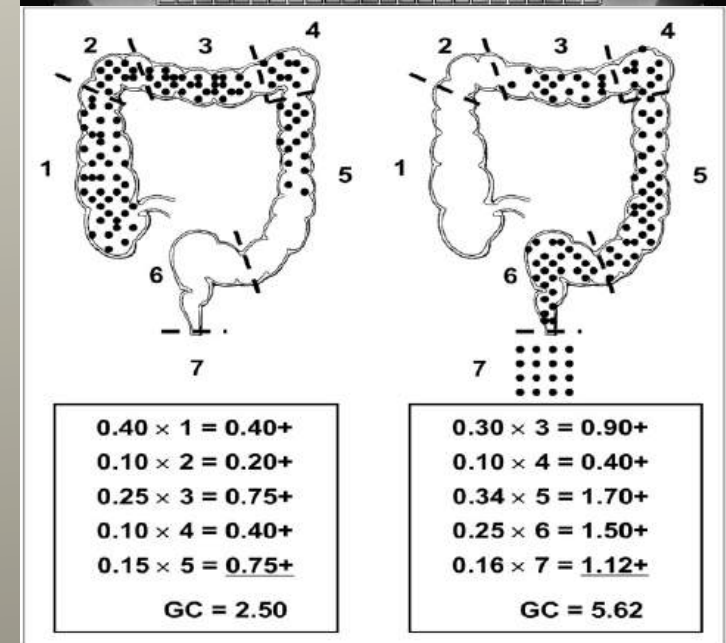
two types

- Increase of transit time

«slow transit constipation»

- Distal outlet obstruction

«constipation by outlet obstruction»



Treatment of constipation

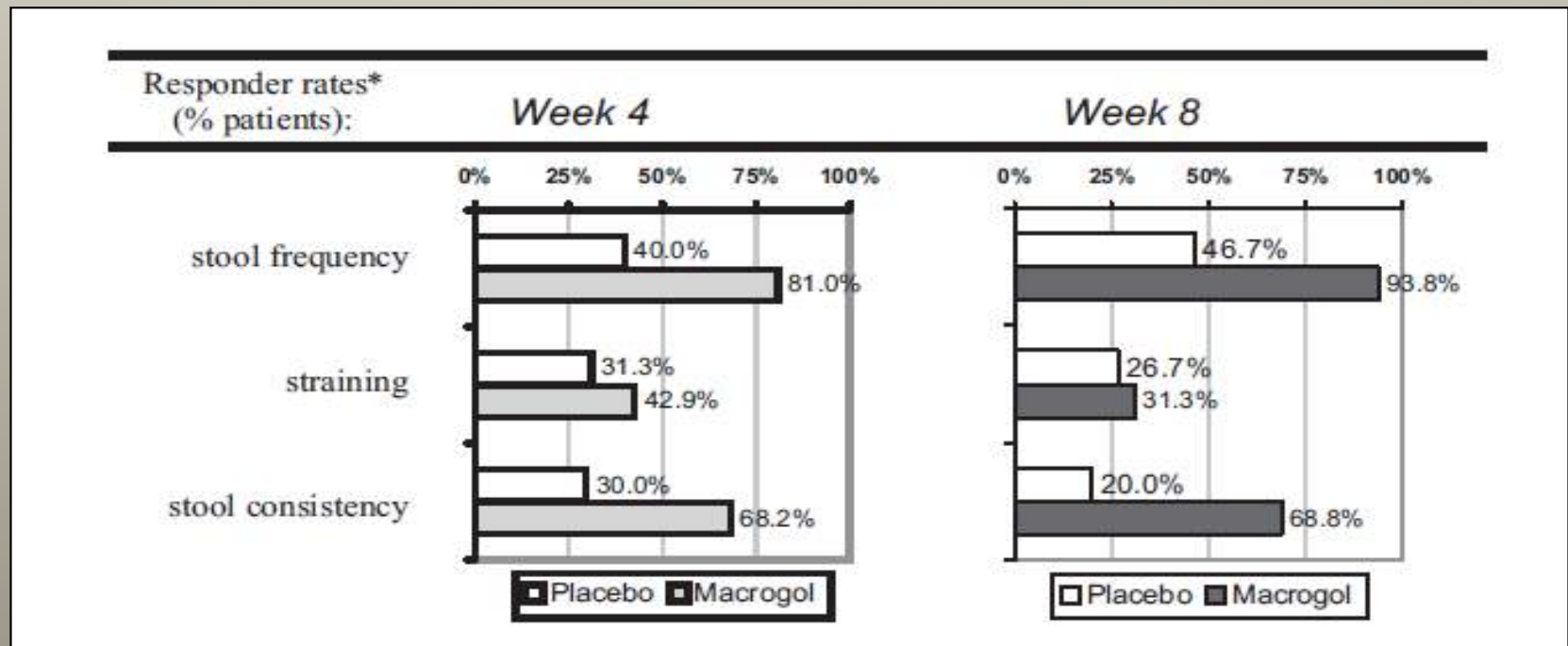
- Stop anticholinergics
- Ballast substances
- Osmotic active substance
  - Lactulose, Sorbitol
- **Macrogol (Movicol®) with sufficient fluids**
- Other laxatives
- Enema
- Procinetics
  - Cisapride: short term effect, no more on the market
  - Erythromycine iv.
    - Cave: Interactions and Torsade de pointes
- (Hemicolectomie)
- (Botulinum toxin if «outlet obstruction»)

(modified, according to Jost WH, 2005; Berthet S et al, Visc Surg 2010)

Treatment of constipation

Iso-osmotic Macrogol-electrolyte solution,
2x/d in 250 ml H₂O

Long-term effect and good tolerance



(Zangaglia R, et al., Mov Disord 2007)

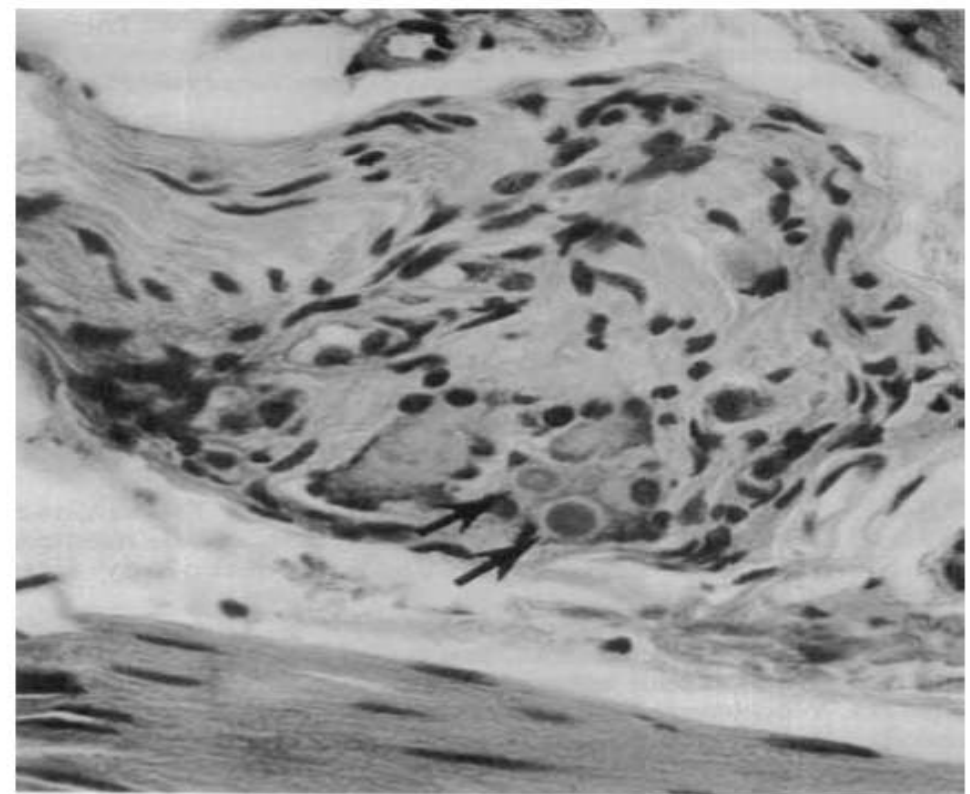
Parkinson's disease and megacolon: Concentric hyaline inclusions (Lewy bodies) in enteric ganglion cells

Article abstract—Concentric hyaline inclusions (Lewy bodies), found in the cytoplasm of pigmented and nonpigmented neurons, are considered characteristic of idiopathic Parkinson's disease. The finding of cytoplasmic inclusions identical to Lewy bodies in ganglion cells of the colonic myenteric plexus in a patient with idiopathic Parkinson's disease and acquired megacolon suggests primary involvement of the enteric nervous system by Parkinson's disease.

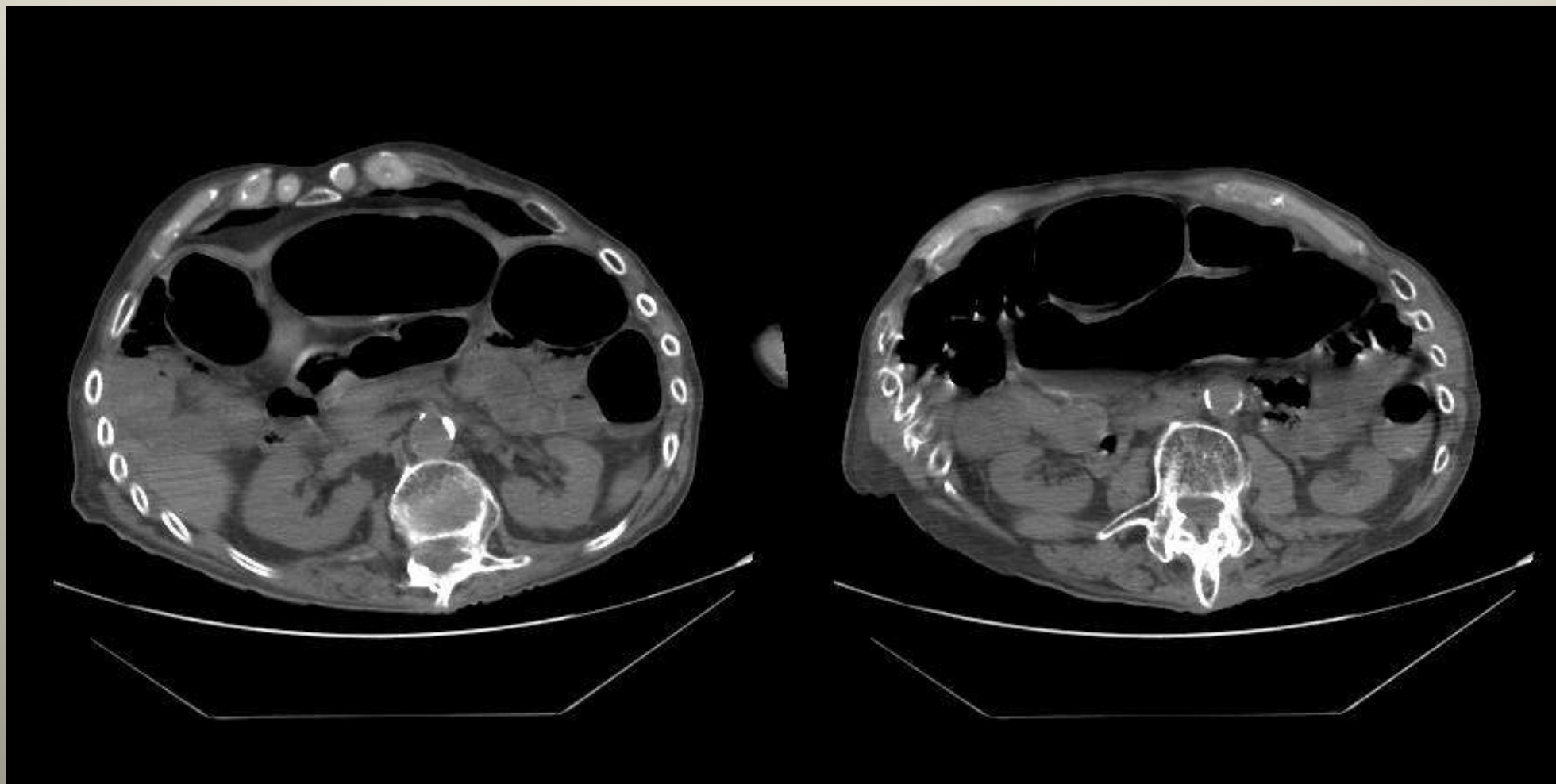
NEUROLOGY 1987;37:1253-1255

W.J. Kupsky, MD; M.M. Grimes, MD; J. Sweeting, MD; R. Bertsch, MD; and L.J. Cote, MD

We suggest that the presence of Lewy bodies in ganglion cells may reflect primary involvement of the enteric nervous system by a degenerative process similar to that occurring in the pigmented nuclei of the CNS in Parkinson's disease. It must be noted, however, that Lewy bodies in the CNS are characteristic but not pathognomonic of Parkinson's disease and have been described as an incidental finding in the CNS of patients without recognized symptoms of Parkinson's disease.¹⁴



Paralytic Ileus 2009



Treatment with Erythromycin iv.

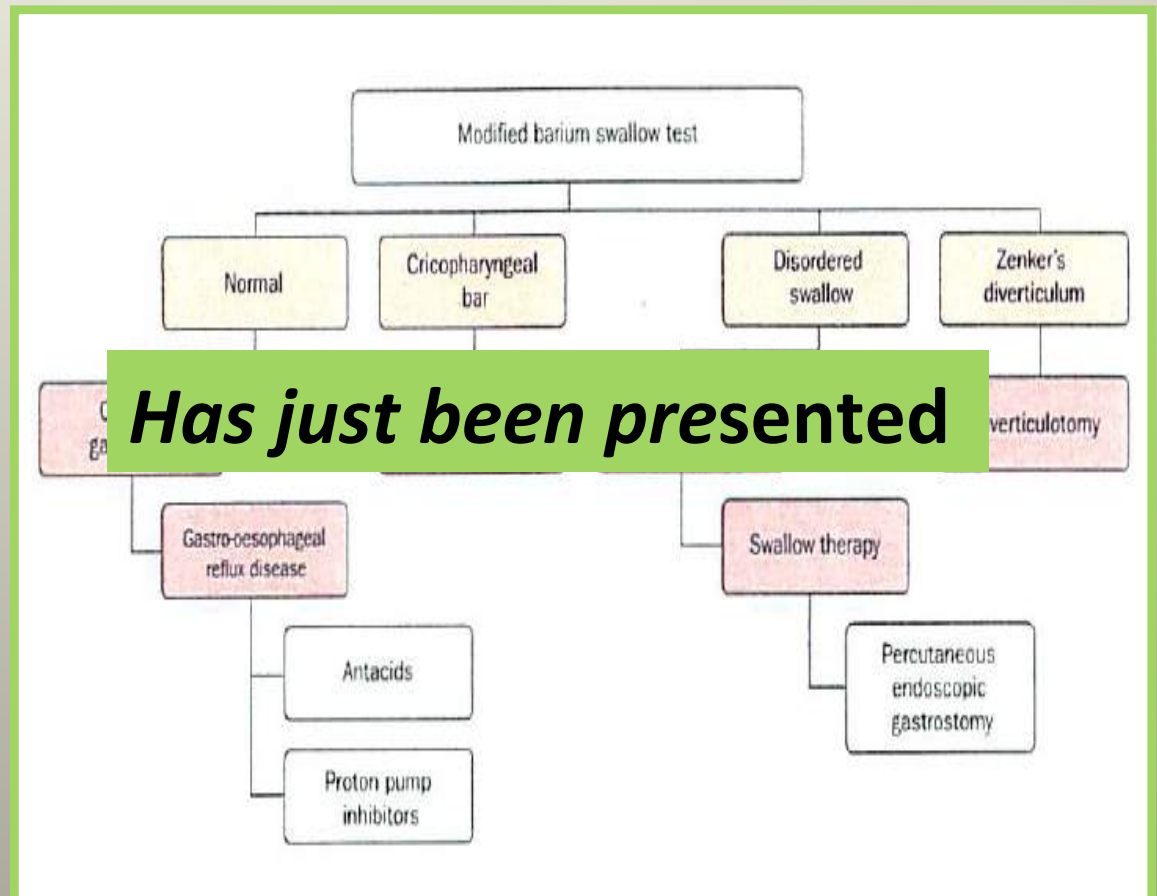
(Barboza JL, et al., Expert Opin Pharmacother 2016)

2011



Dysphagia

- Test with blue methylen
- Video fibroscopy
- Thickening of fluids
  - (Nutilis®)
  - Mush food
- PEG?++

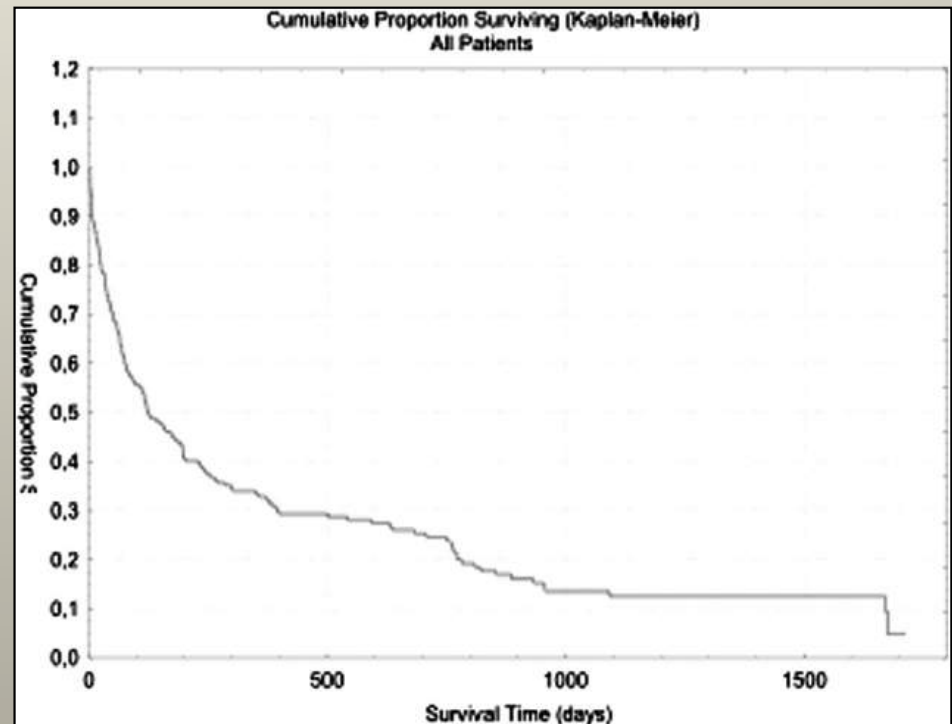


(Flow chart by Pfeifer RF, Lancet Neurol 2003)

Dysphagia

Indication of percutaneous endoscopic Gastrostomy (PEG)?

- Retrospectiv study
- n = 201
- 30-days-Mortality: 20%
- Mean survival time: 123 days
- PD pts. : 233 days



(Malmgren A, et al., Food Nutr Res 2011)

Take home messages

- Cardiovascular S.: early & late involvement
- MIBG-SPECT findings: mysterious (outside of Braak routes)
- Therapeutic dilemma: to treat diurnal orthostatic hypotension and/or nocturnal supine hypertension
- Midodrine: efficient
- !!: QT prolongation (disease *and* treatment)

Take home messages

- GIT: early and late involvement
- LB / α syn in submucosa, but not in mucosa
  - Transitory phenomenon (“Tornado”?)
- GIT = one (among others) entry or starting points?
- Constipation: even a risk factor
- Dysphagia and (rarely) paralytic ileus: late symptoms

Take home messages

- GIT: early and late involvement
- LB / α syn in submucosa, but not in mucosa
  - Transitory phenomenon (“Tornado”?)
- GIT = one (among others) entry or starting points?
- Constipation: early and late symptom
- Dysphagia and symptoms

Gap between knowledge and clinical applicability

More controlled studies urgently needed

Thank you



- **CHL:** L Longhino, G Hipp, V Pieri, J Weber
- **LCSB:** P Antony, R Balling, A Baumuratov, M Buttini, M Ostaszewski
- **IBBL:** L Antunes, S Frasquilho
- **LIH:** N Sauvageot, M Vaillant
- **Rush University:** CG Goetz, K Shannon
- **and many more**

