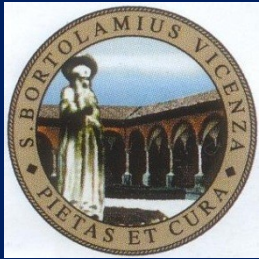


Approach to refractory GERD (PPI Failure)



Giovanni CATAUDELLA

U.O.GASTROENTEROLOGIA ed ENDOSCOPIA DIGESTIVA

OSPEDALE S.BORTOLO - ULSS 6 VICENZA

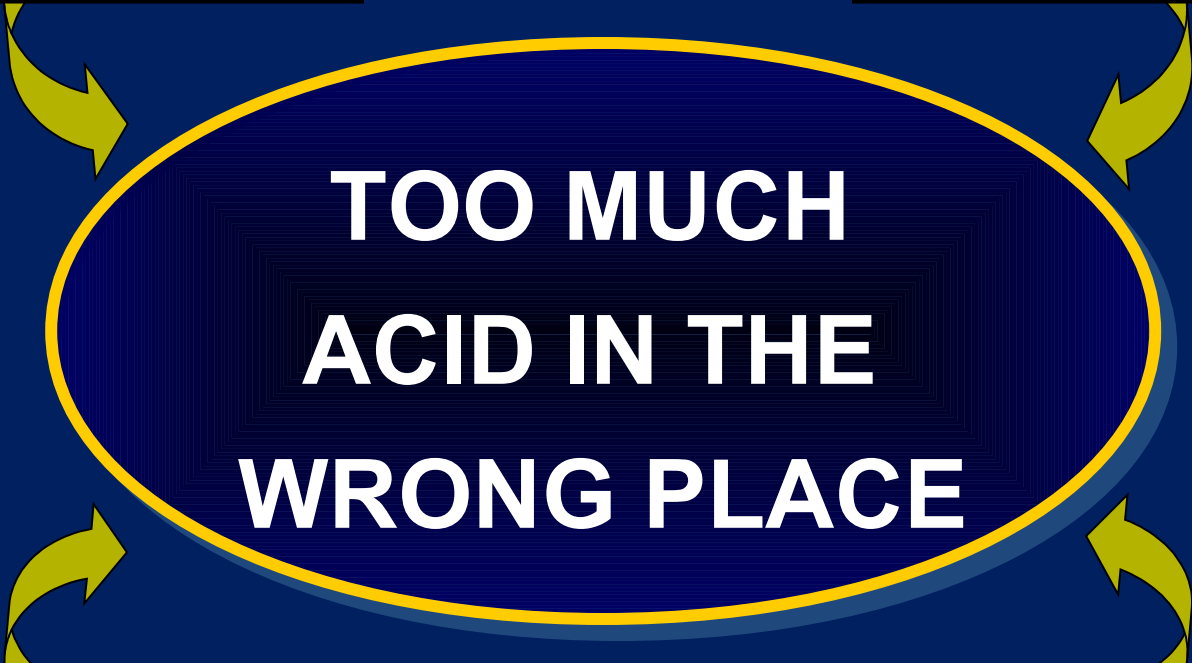
**Abnormal
esophageal
clearing**

**Insufficient
antireflux
barrier**

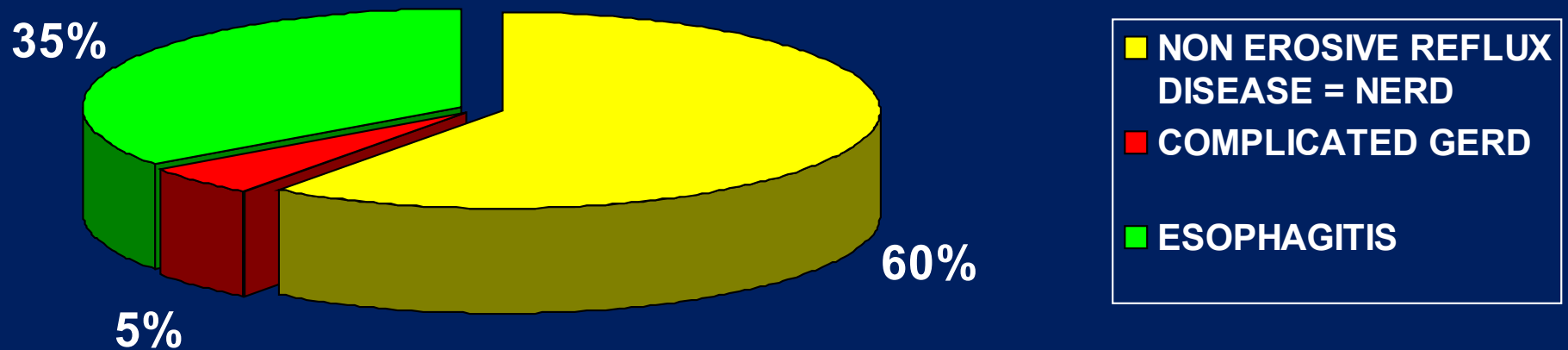
**TOO MUCH
ACID IN THE
WRONG PLACE**

**Altered
gastric
emptying**

**Diet, drugs
smoking, etc**



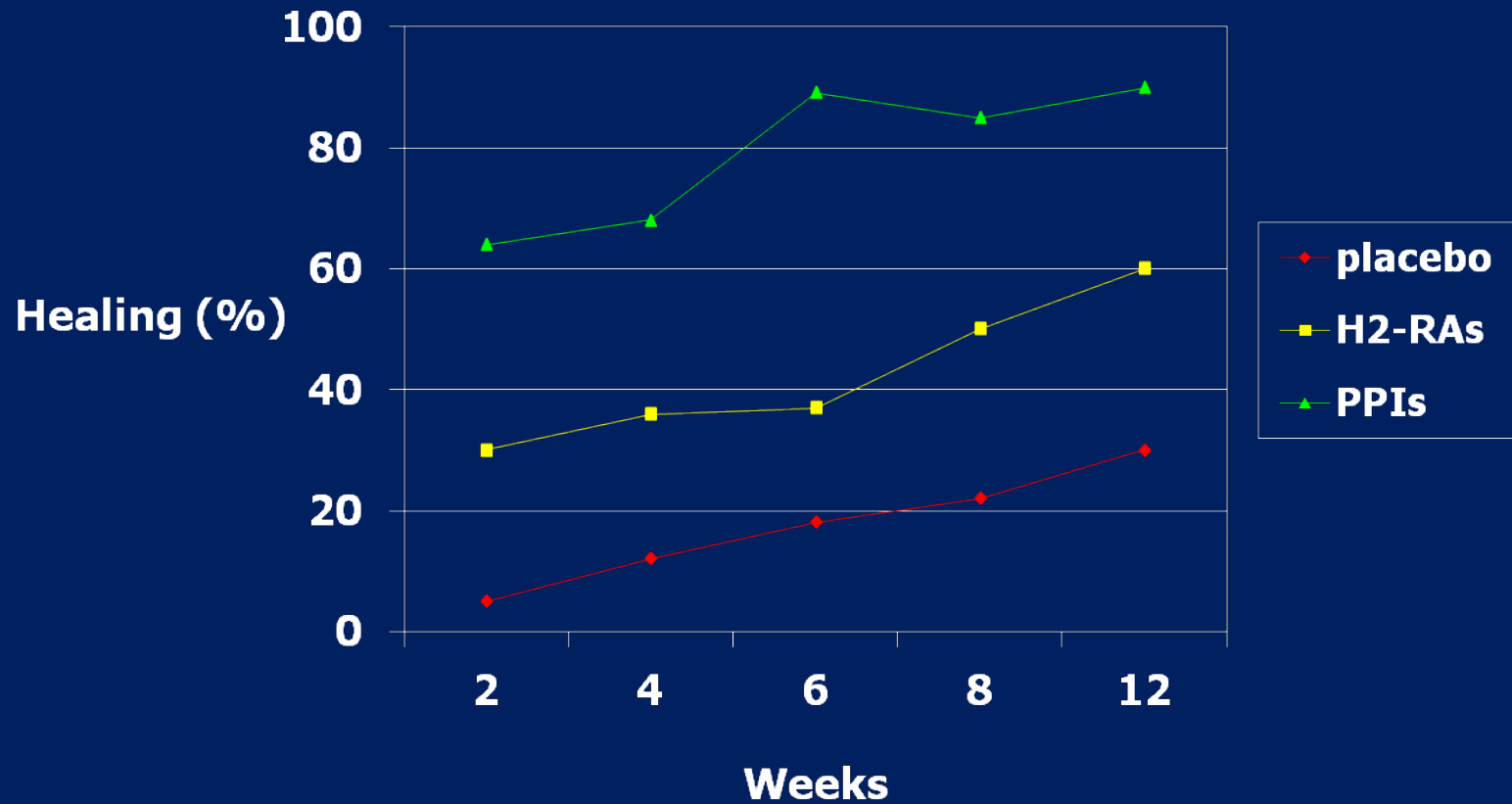
Clinical spectrum of GERD



DeVault e Castell, 1995

Richter, 1992

Efficacy of PPIs in reflux esophagitis



Chiba et al, Gastroenterology, 1997

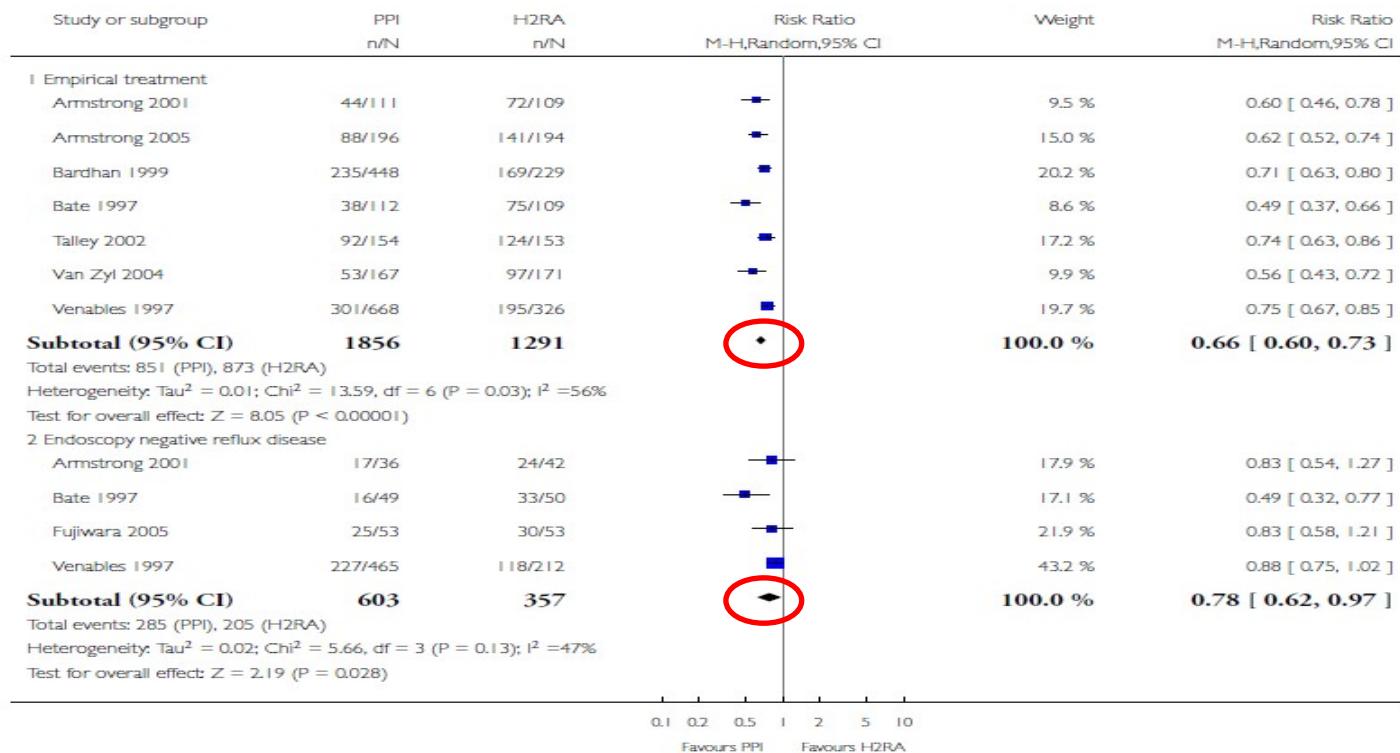
PPIs vs H2RA in NERD pts with Heartburn remission (Cochrane Review, 2010)

Analysis 4.1. Comparison 4 PPI versus H2RA, Outcome 1 Heartburn remission.

Review: Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease

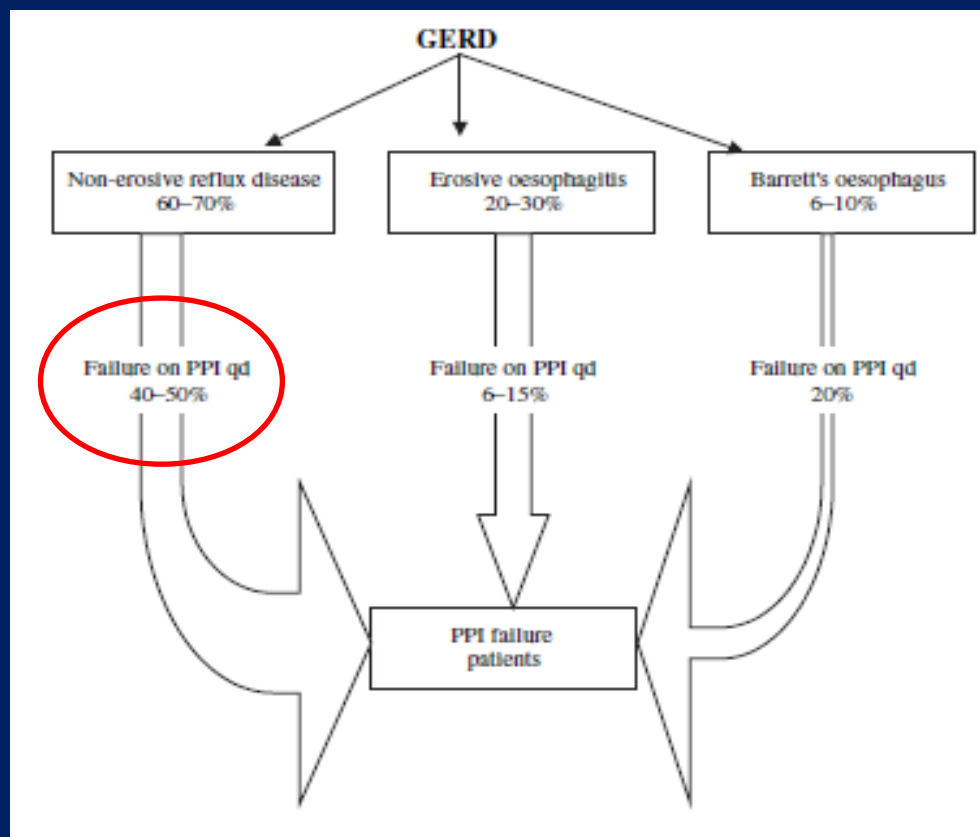
Comparison: 4 PPI versus H2RA

Outcome: 1 Heartburn remission



Refractory GERD (PPI Failure) definition:

Lack of satisfactory symptomatic response to PPI once a day in pts with GERD

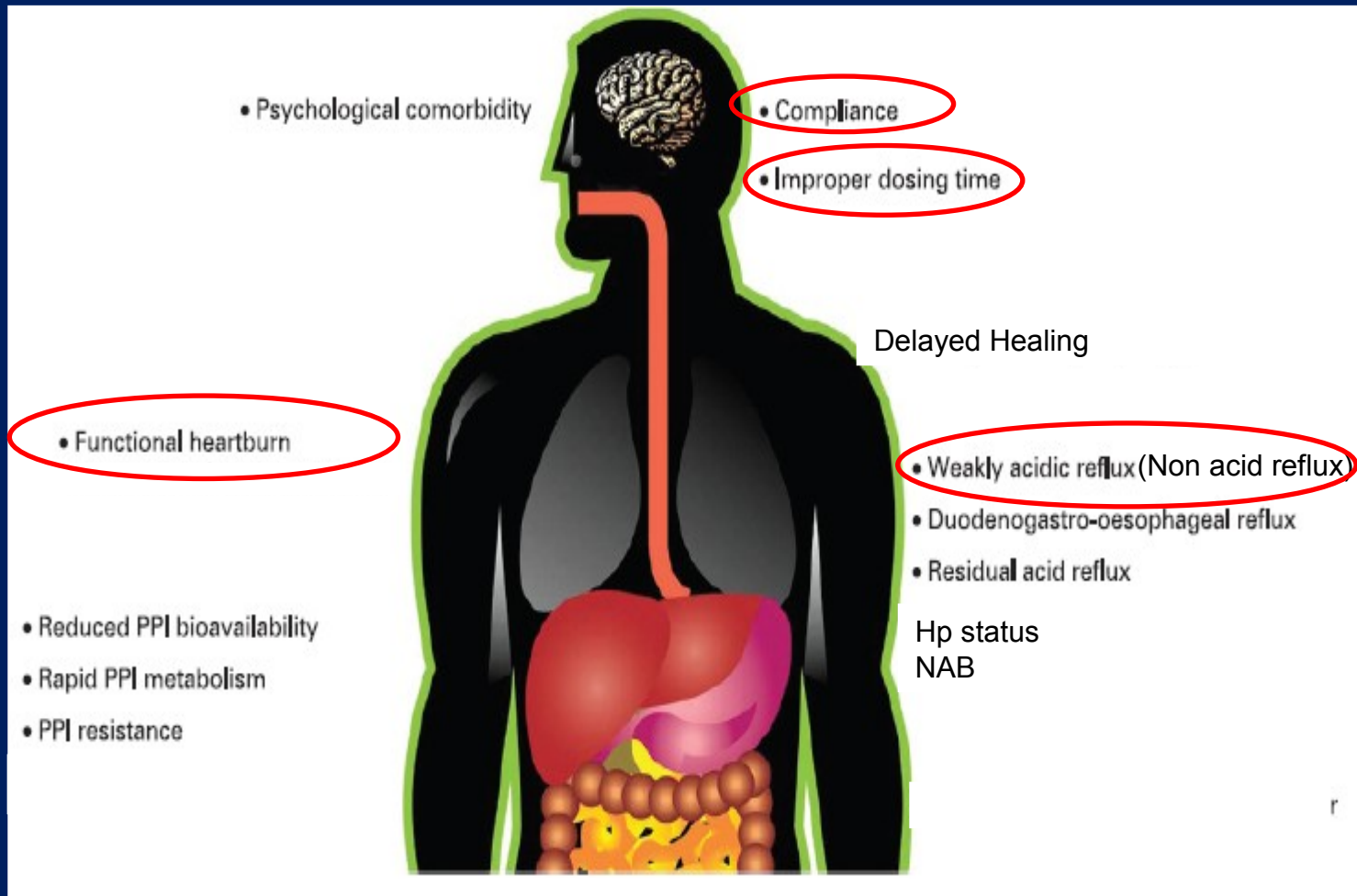


R.Fass et al. APT 2005; 22:79-94

Inadomi JM et al. Am J Gastroenterol 2003; 98:1940

Refractory GERD

UNDERLYING MECHANISMS OF PPI FAILURE



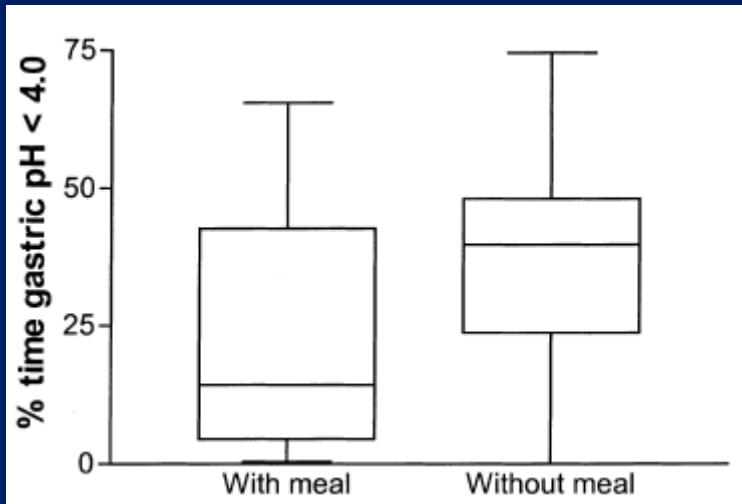
Refractory GERD

UNDERLYING MECHANISMS OF PPI FAILURE:

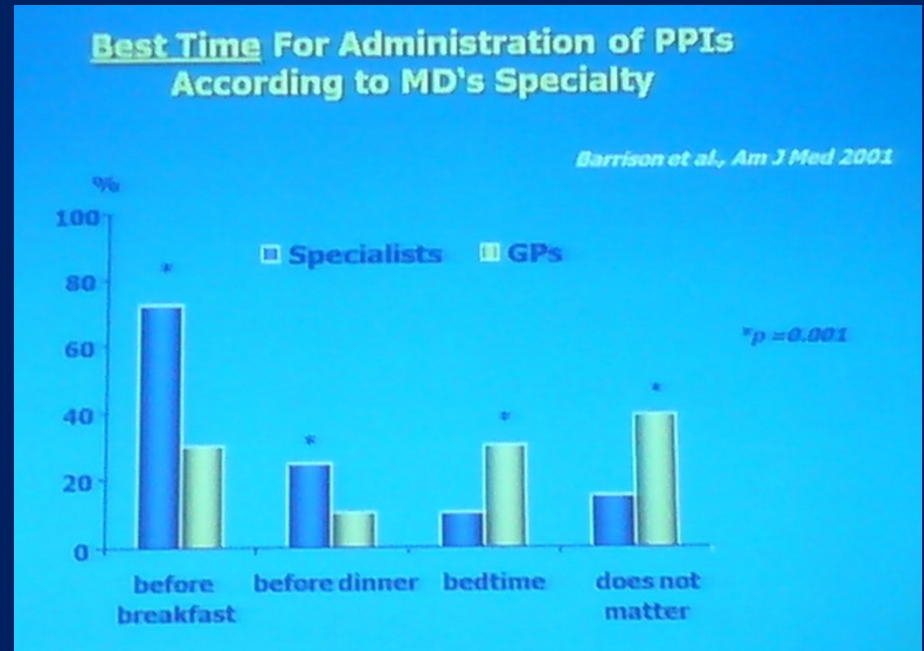
Improper dosing time

Superior pH control when a PPI is taken 30 min. before breakfast

Patients not received adequate instructions



Hatlebakk JG et al. APT Aliment Pharmacol Ther 2000; 14:1267



Barrison et al. Am J Med ; 2001

Refractory GERD

UNDERLYING MECHANISMS OF PPI FAILURE

Compliance

Poor compliance with PPIs is common in patients with GERD

Fass R. et al. Curr Gastroenterol Rep 2008; 10:252

Factors influencing compliance:

- presence or absence of symptoms
- severity of symptoms
- personal preference about when to take treatment
- knowledge about the treated disorder
- desire for personal control
- the prescribed drug (taste, consistency, etc)
- side effects
- number of pills per day
- concomitant therapies
- age
- personality
- socioeconomic status
- healthcare coverages

Hungin AP et al. Br J Gen Pract 1999; 49:463

Refractory GERD (PPI Failure) Prevalence

Most patients with PPI failure are:

NERD (~40%)

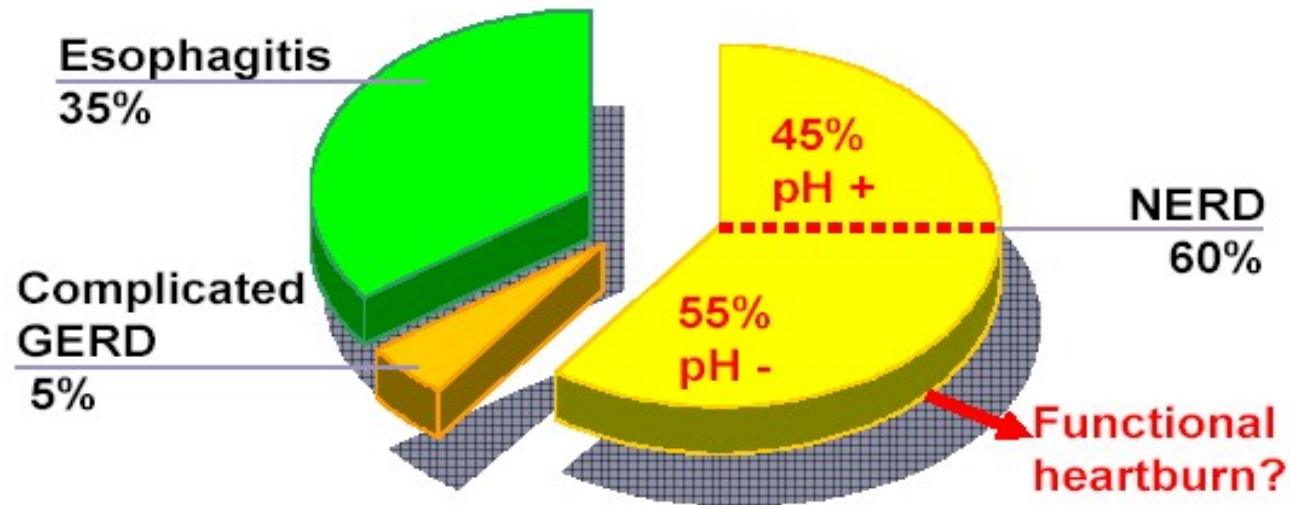
or

FH (~60%)

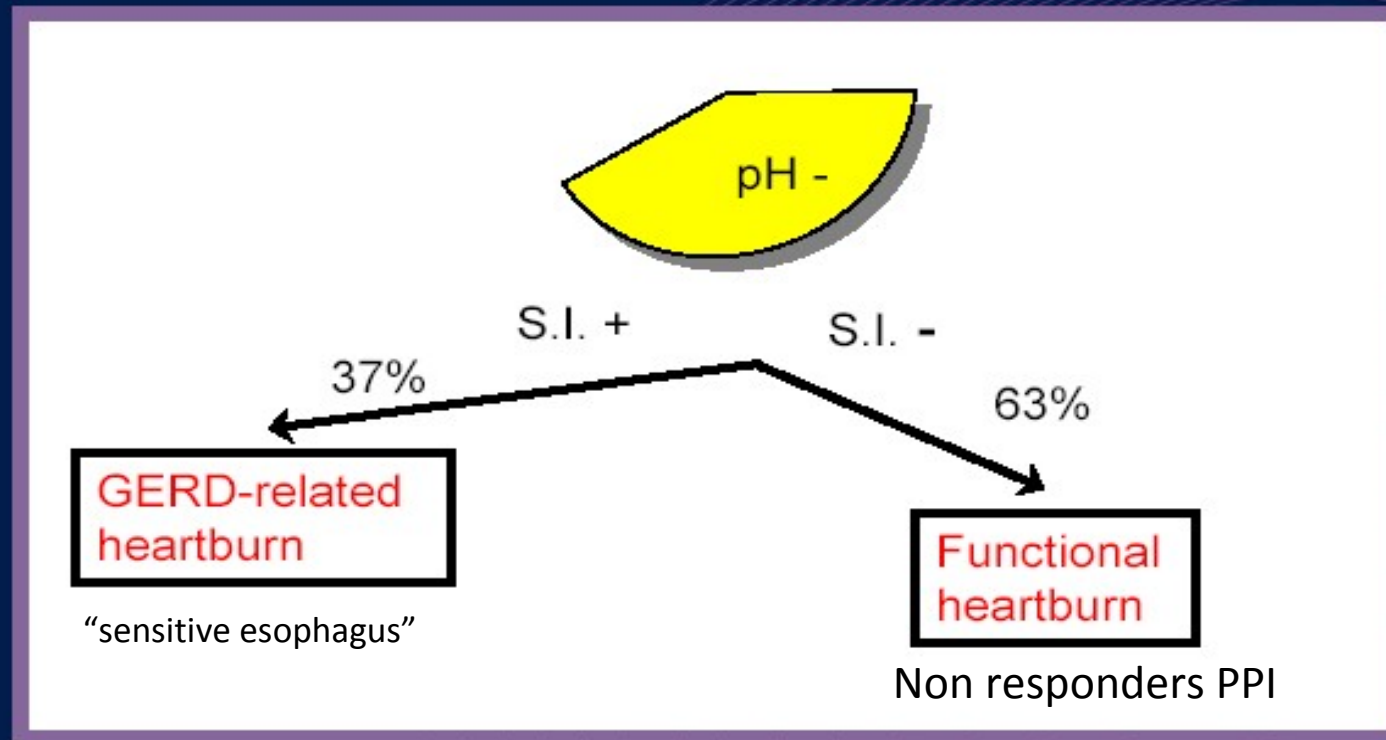
the most common cause
for PPI failure

Inadomi JM et al. Am J Gastroenterol 2003; 98:1940

Endoscopic + pH-metry categorization of GERD patients

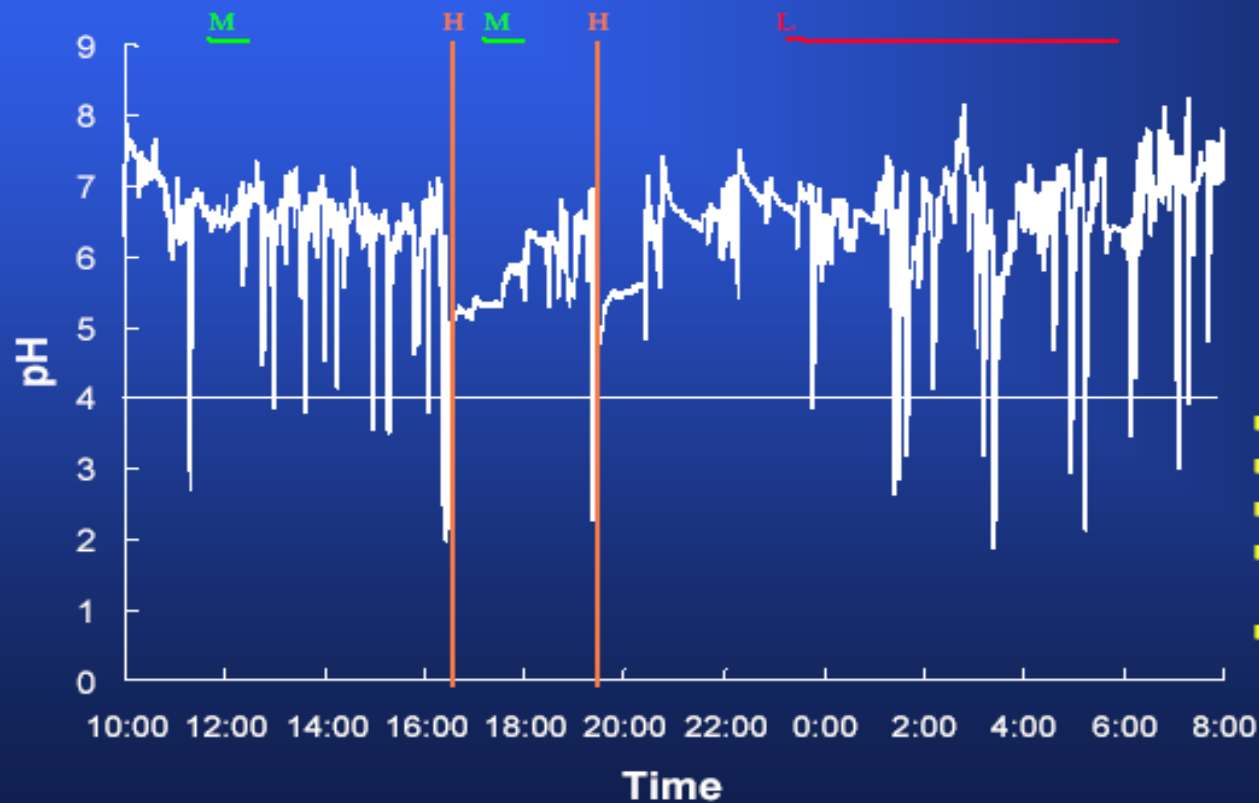


Subcategorization of pH-negative NERD patients according to Symptom Index (SI)



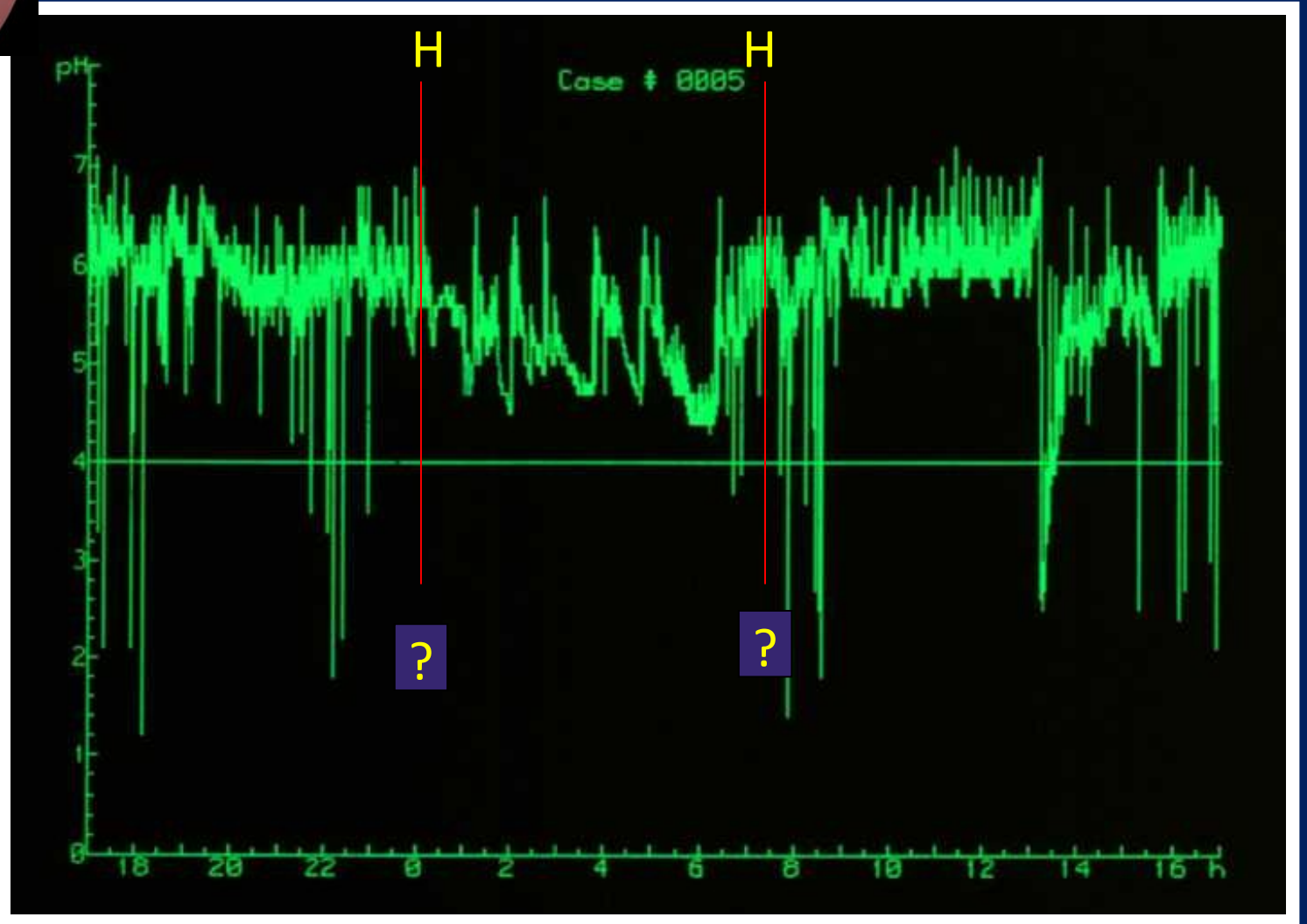


ESOPHAGEAL pH RECORDING SYMPTOM EVENTS



- Symptom index.
- Symptom sensitivity index.
- Binomial symptom index.
- Symptom-association probability.
- Acid burden.

“sensitive esophagus”



FUNCTIONAL HEARTBURN (FH)

Rome criteria III definition

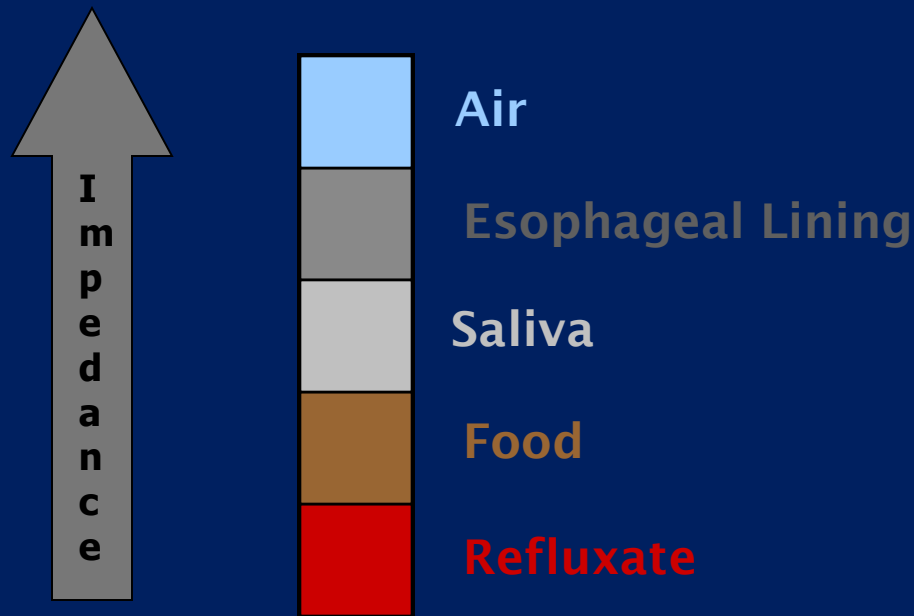
1. Burning retrosternal discomfort or pain
 2. Absence of evidence of GERD as the cause of symptoms
 3. Absence of histopathology-based esophageal motility disorders
- with all three criteria fulfilled for the last three months and symptom onset at least six months prior to diagnosis

Limitations of esophageal pH-monitoring

- Invasive technique
- Low patient's compliance
- Technical failure of the measuring system
- Inability to identify non-acid reflux
- Variability of reflux events from day to day

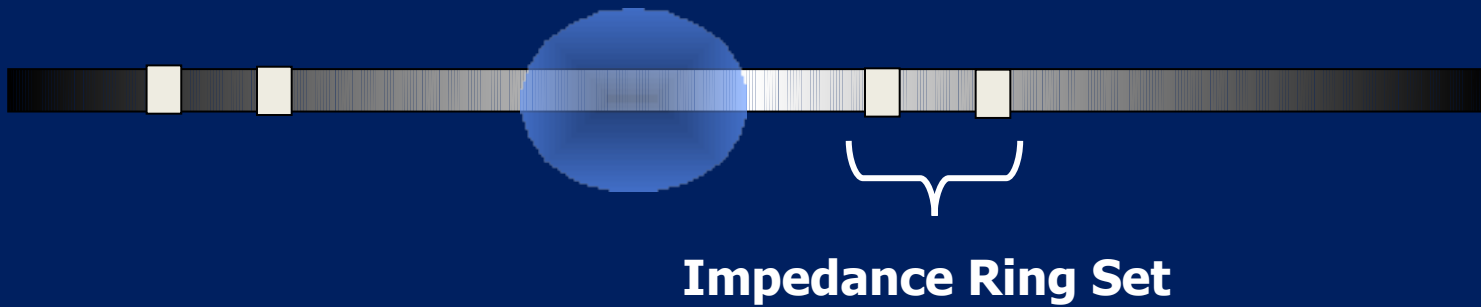
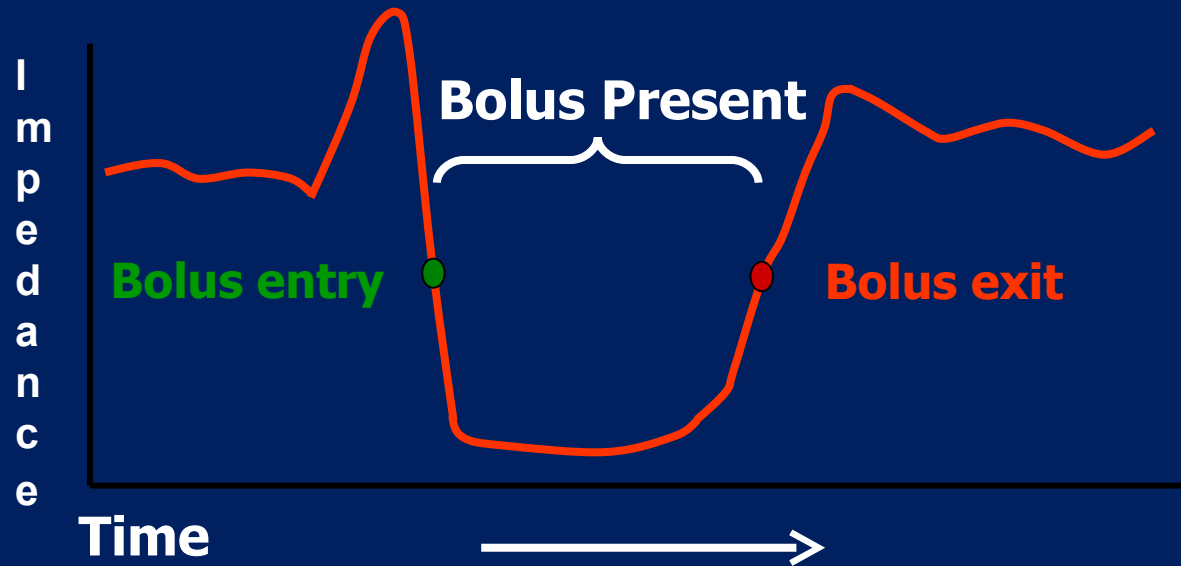
The Impedance Scale definition

Low Conductivity = High impedance

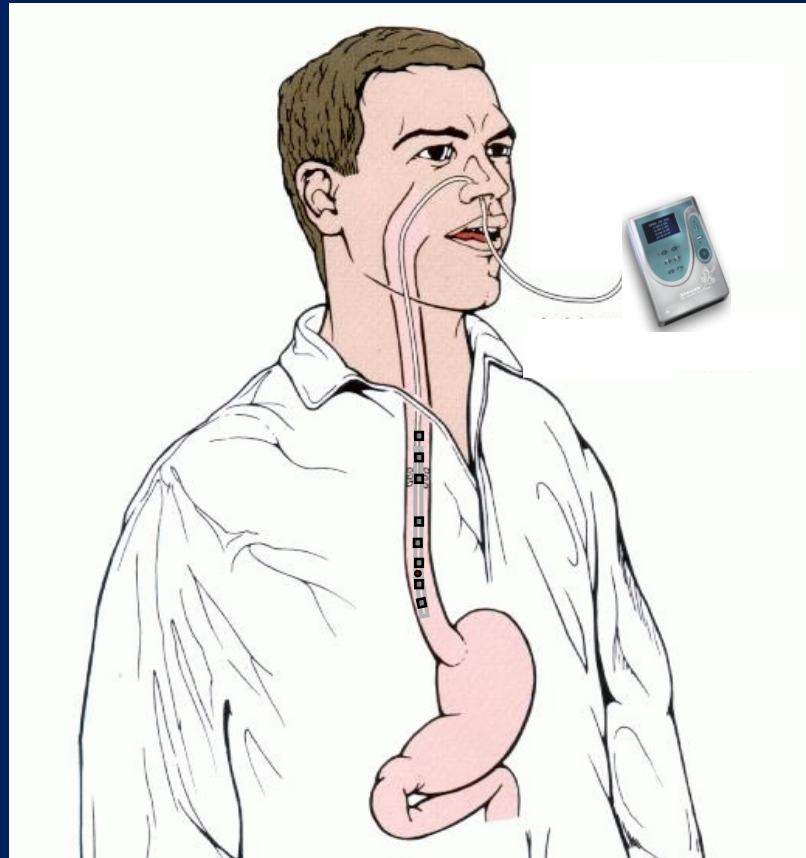


High Conductivity = Low impedance

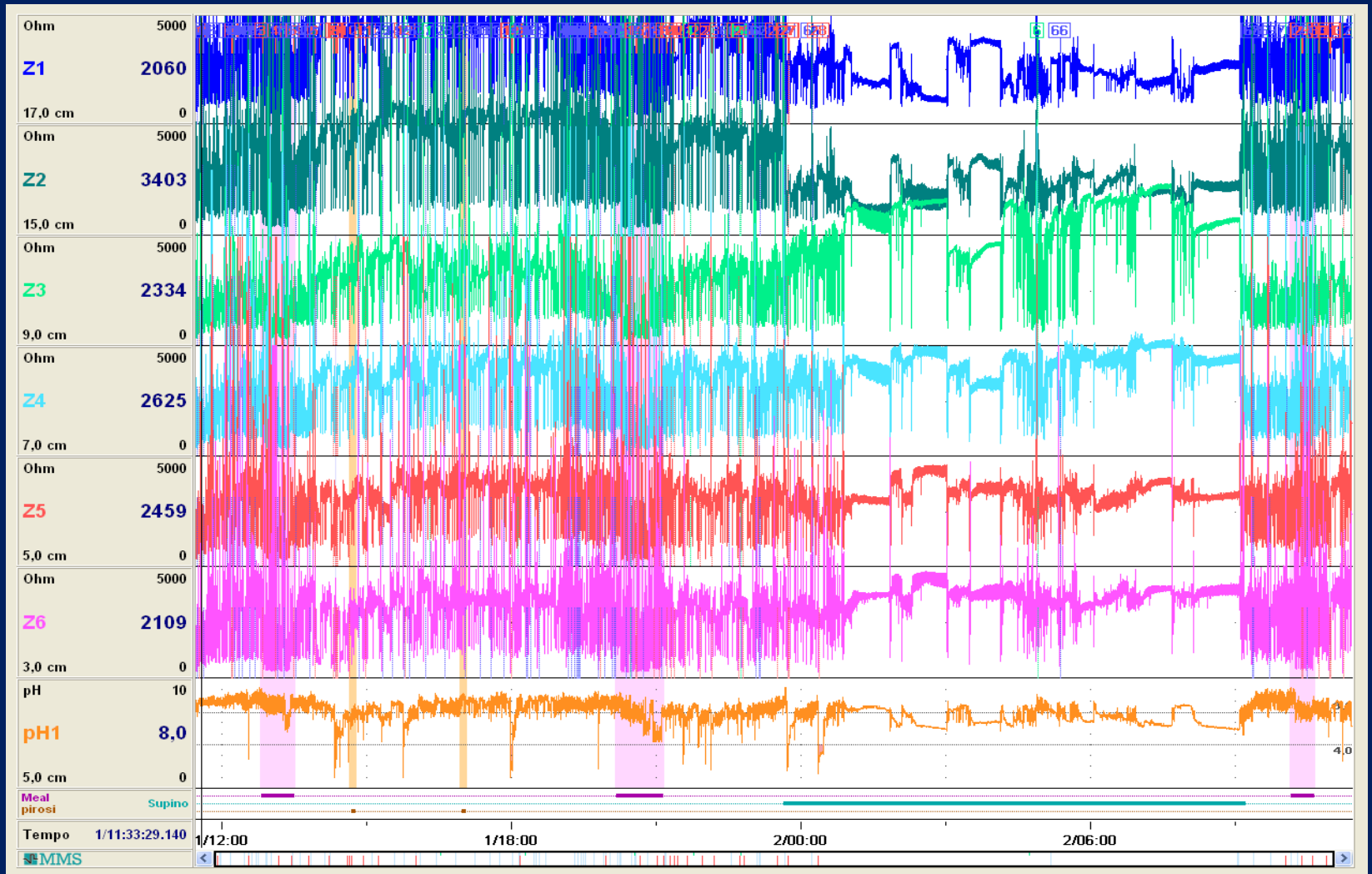
Impedance definition



24-hour ambulatory pH-impedance (pH-MII)

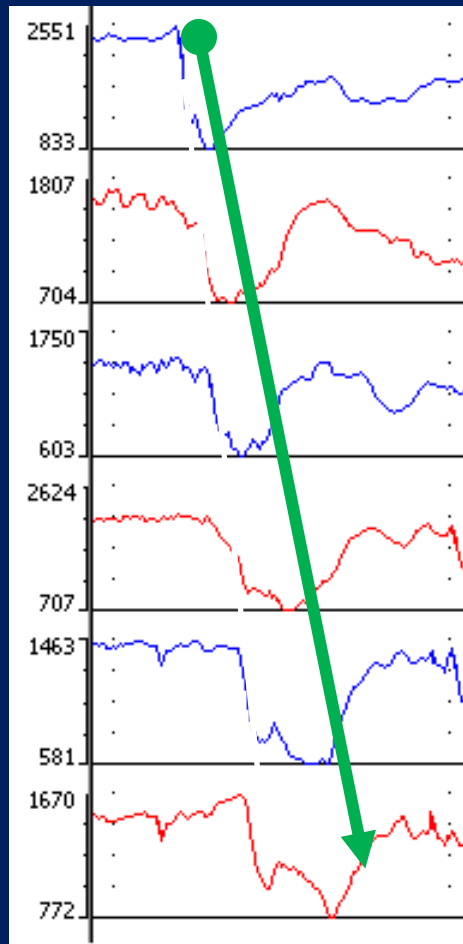


Normal pattern of pH-MII

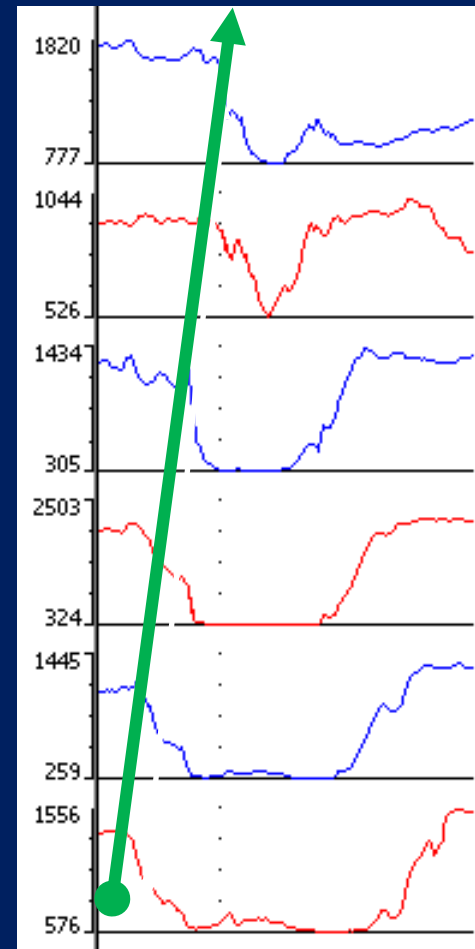


MII Detected Bolus Movement

Antegrade-Swallow



Retrograde-Reflux



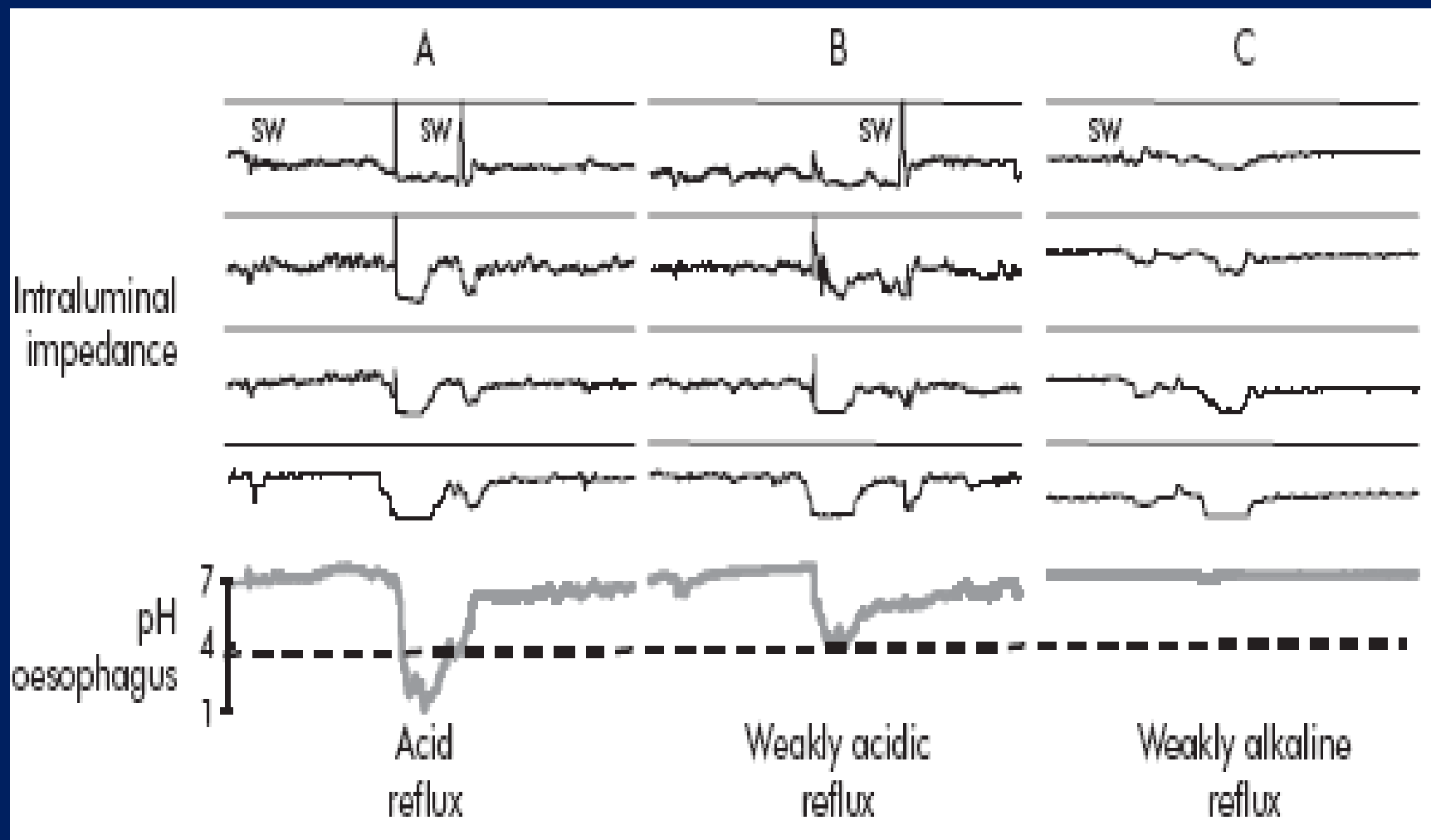
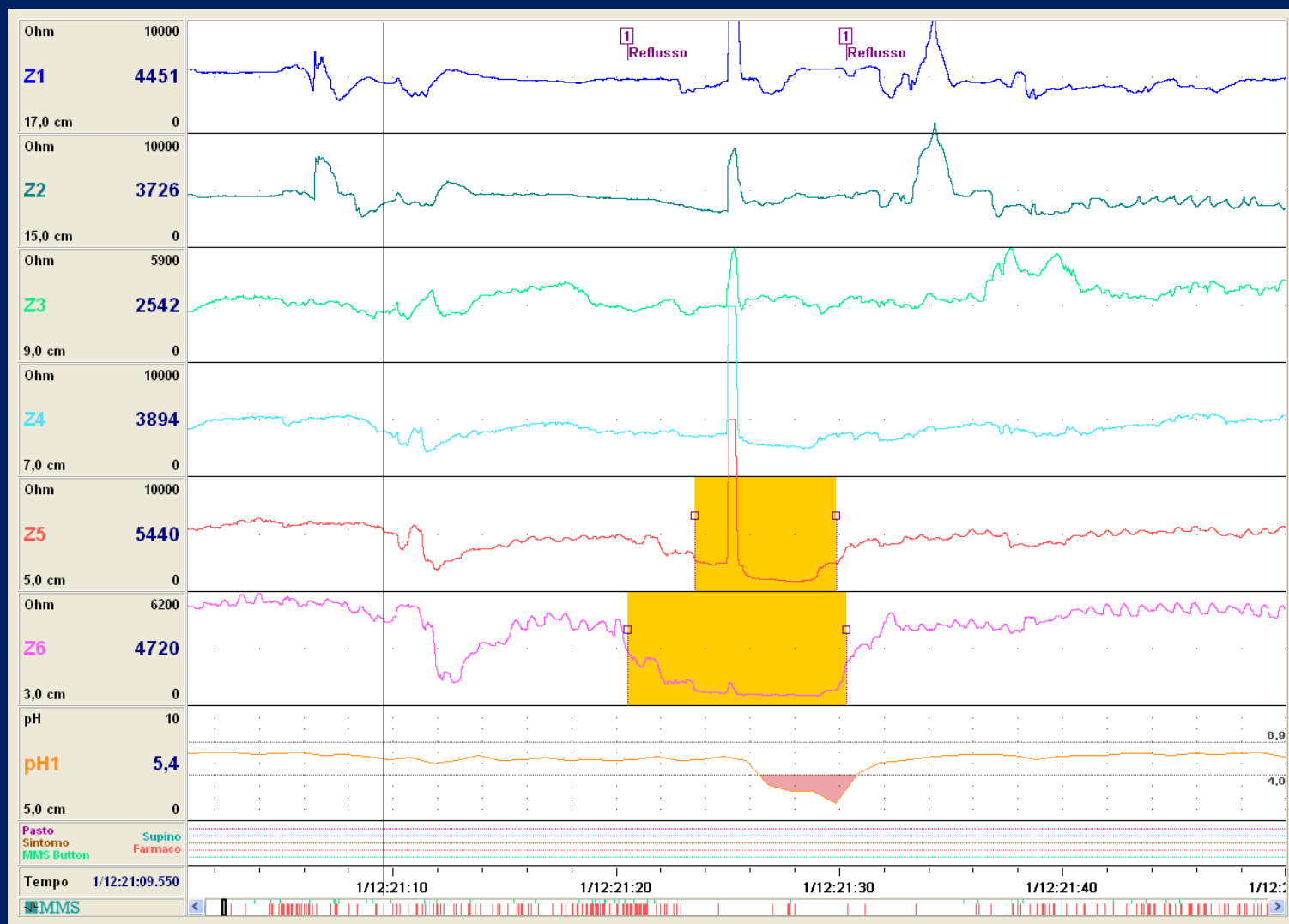
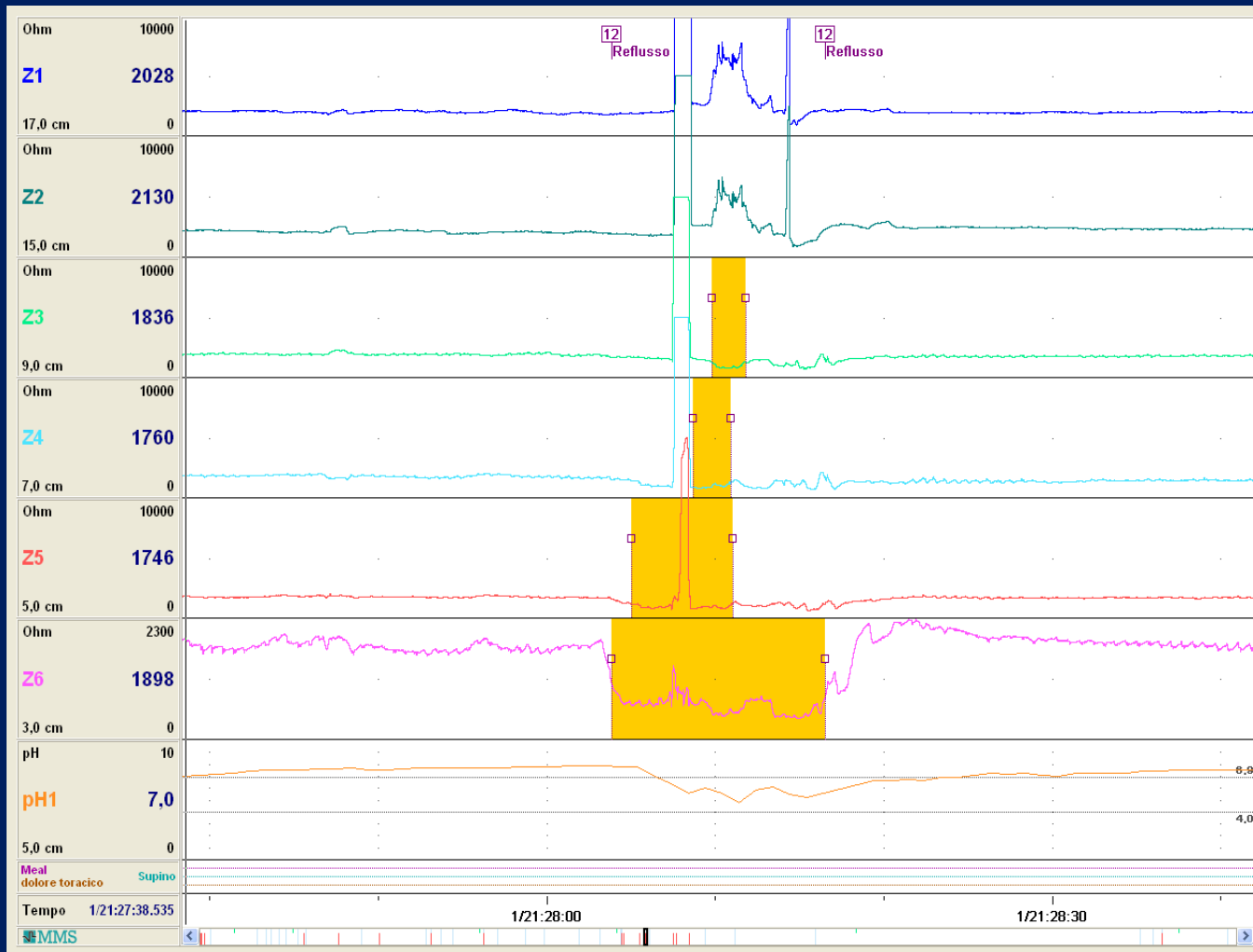


Figure 6 Definitions of reflux are based on the pH of the refluxate. Acid reflux (A) is defined as reflux that reduces oesophageal pH to below 4 or reflux that occurs when oesophageal pH is already below 4. Superimposed acid reflux is a subcategory of acid reflux. Weakly acidic reflux (B) is defined as a pH fall of at least 1 unit where the pH does not fall below 4, and a pH of 7 is the cut off between "weakly acidic" and "non-acid reflux". Weakly alkaline reflux (C) is defined as a reflux episode during which nadir oesophageal pH does not drop below 7.

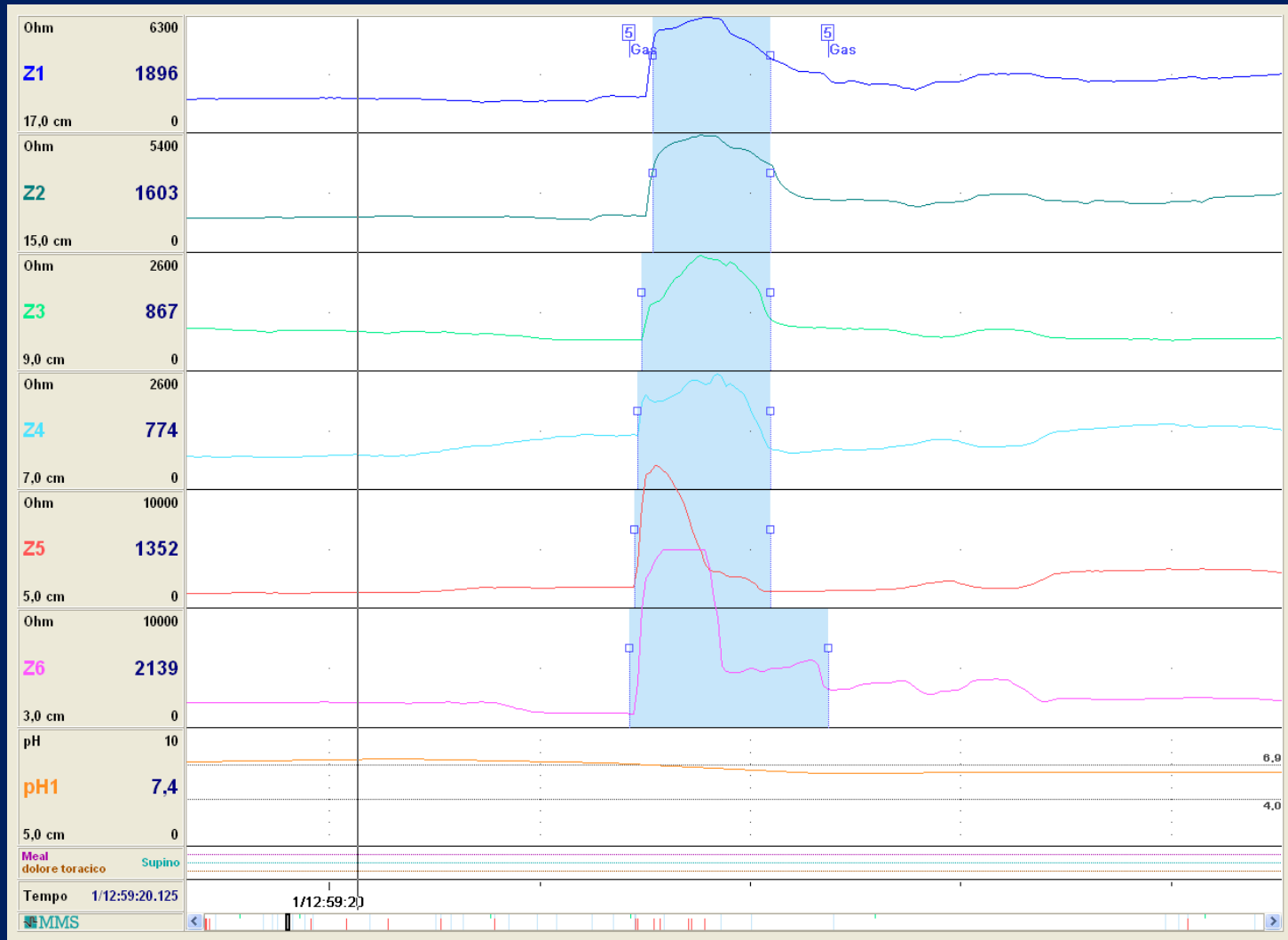
Mixed acid reflux



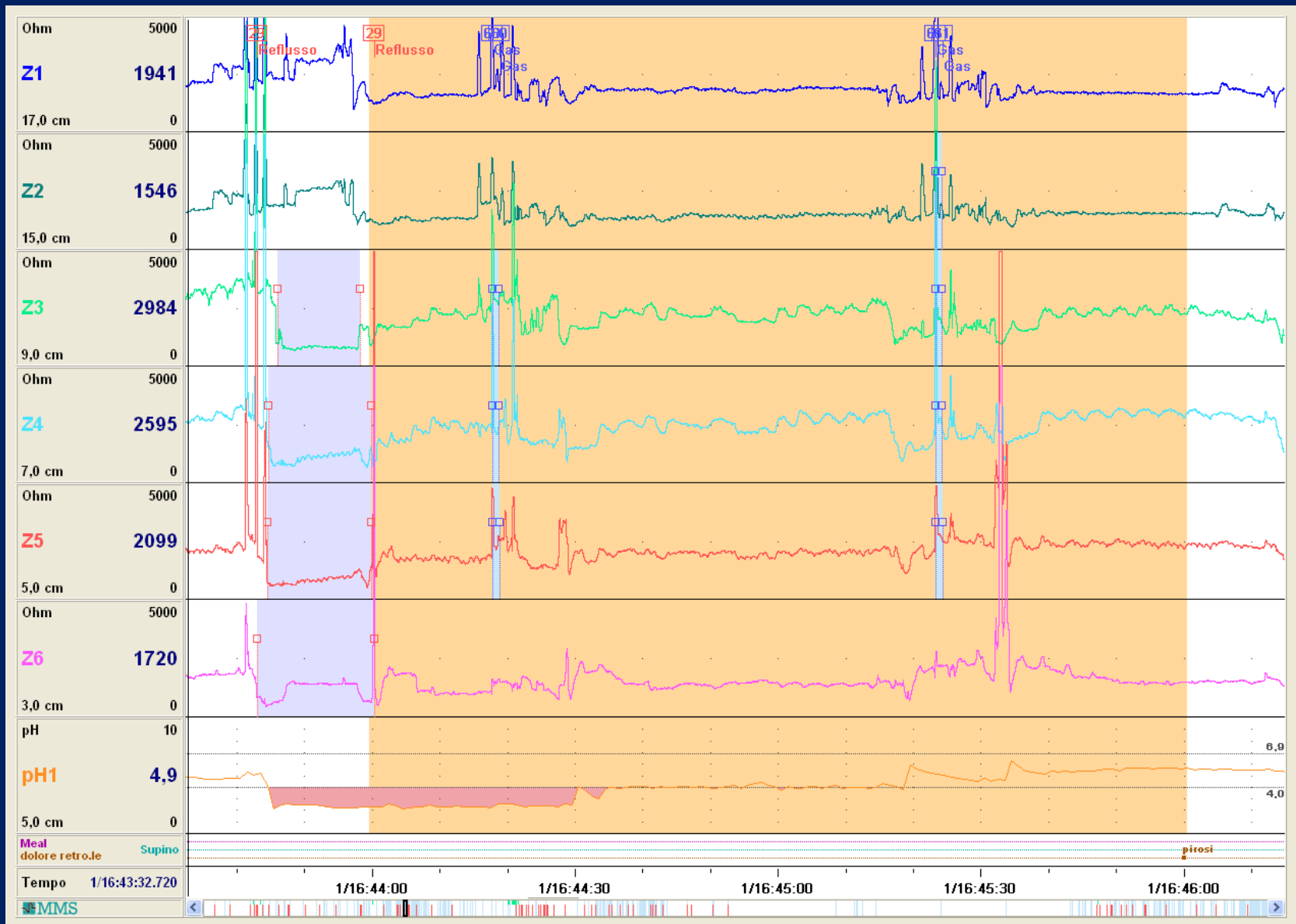
Mixed weakly acid reflux



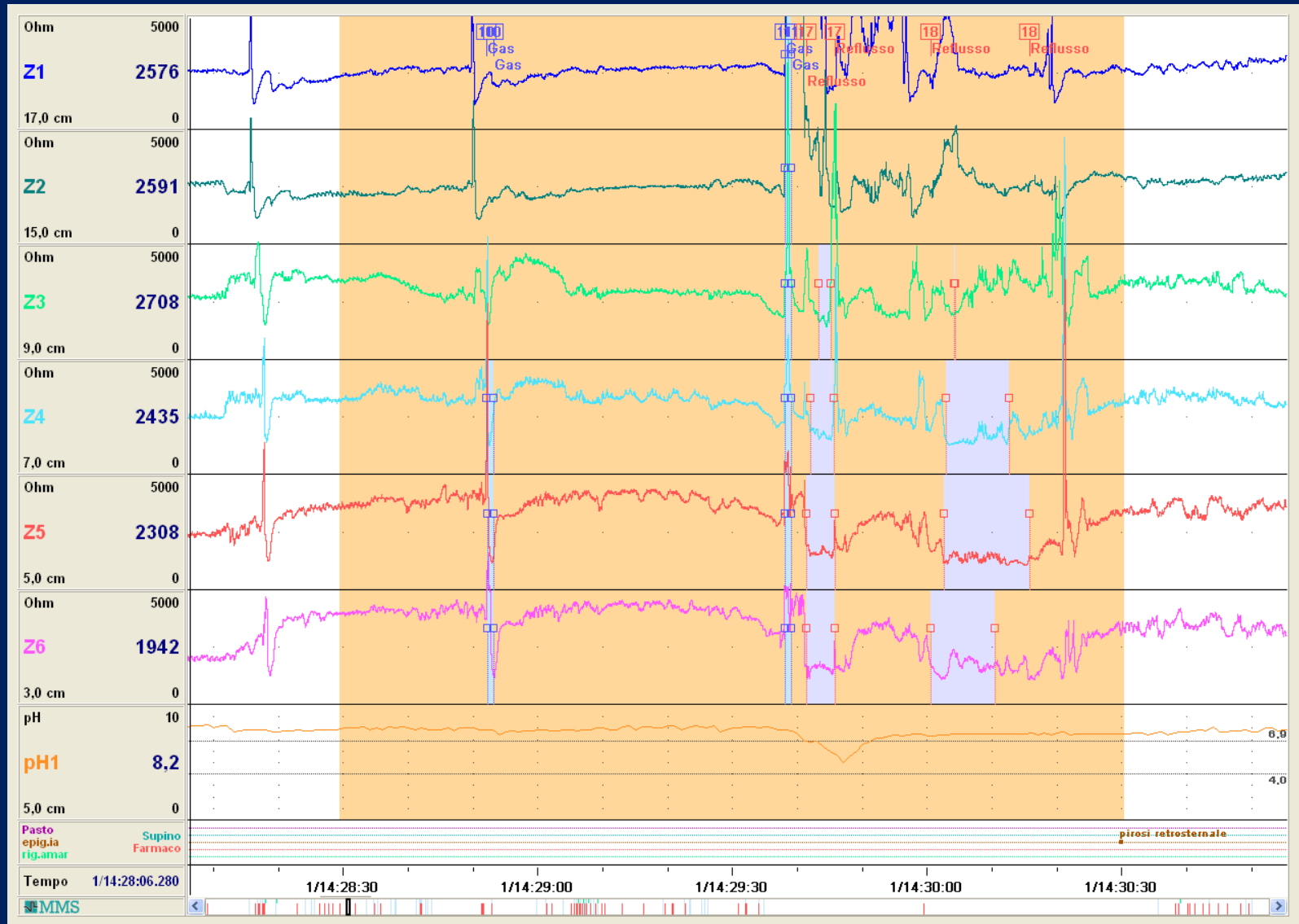
Gas reflux



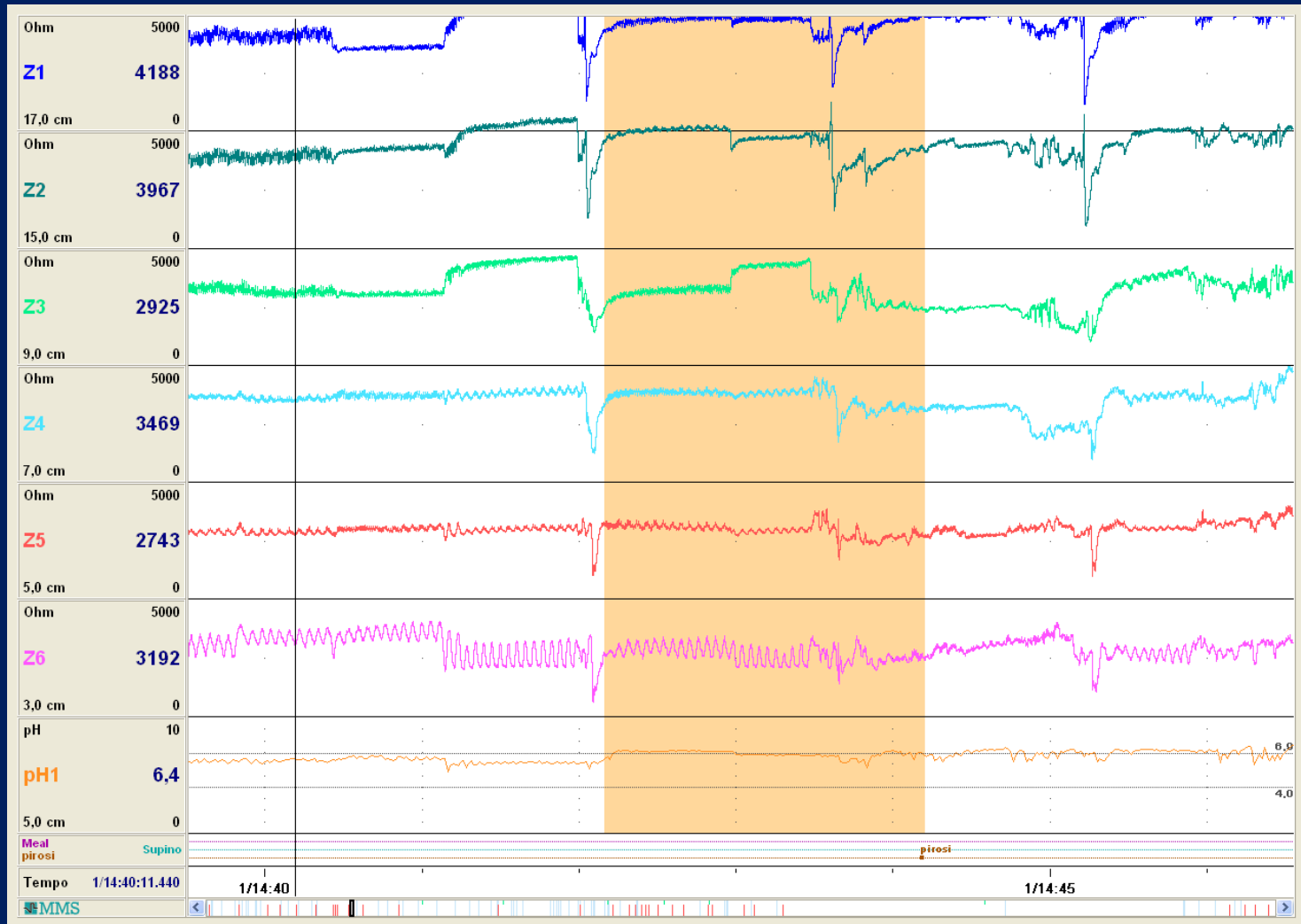
Acid Reflux → Heartburn



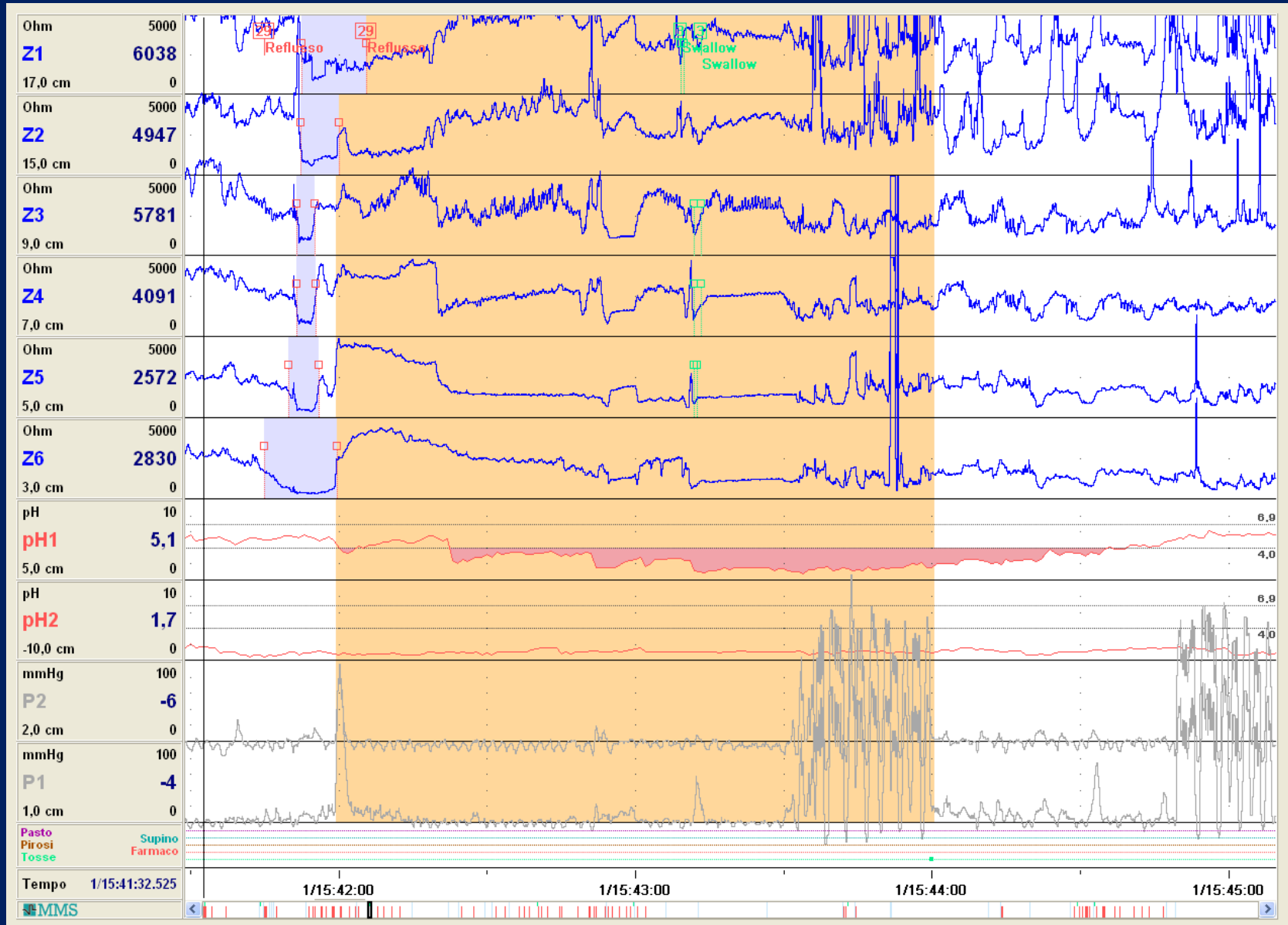
Weakly acid reflux → heartburn



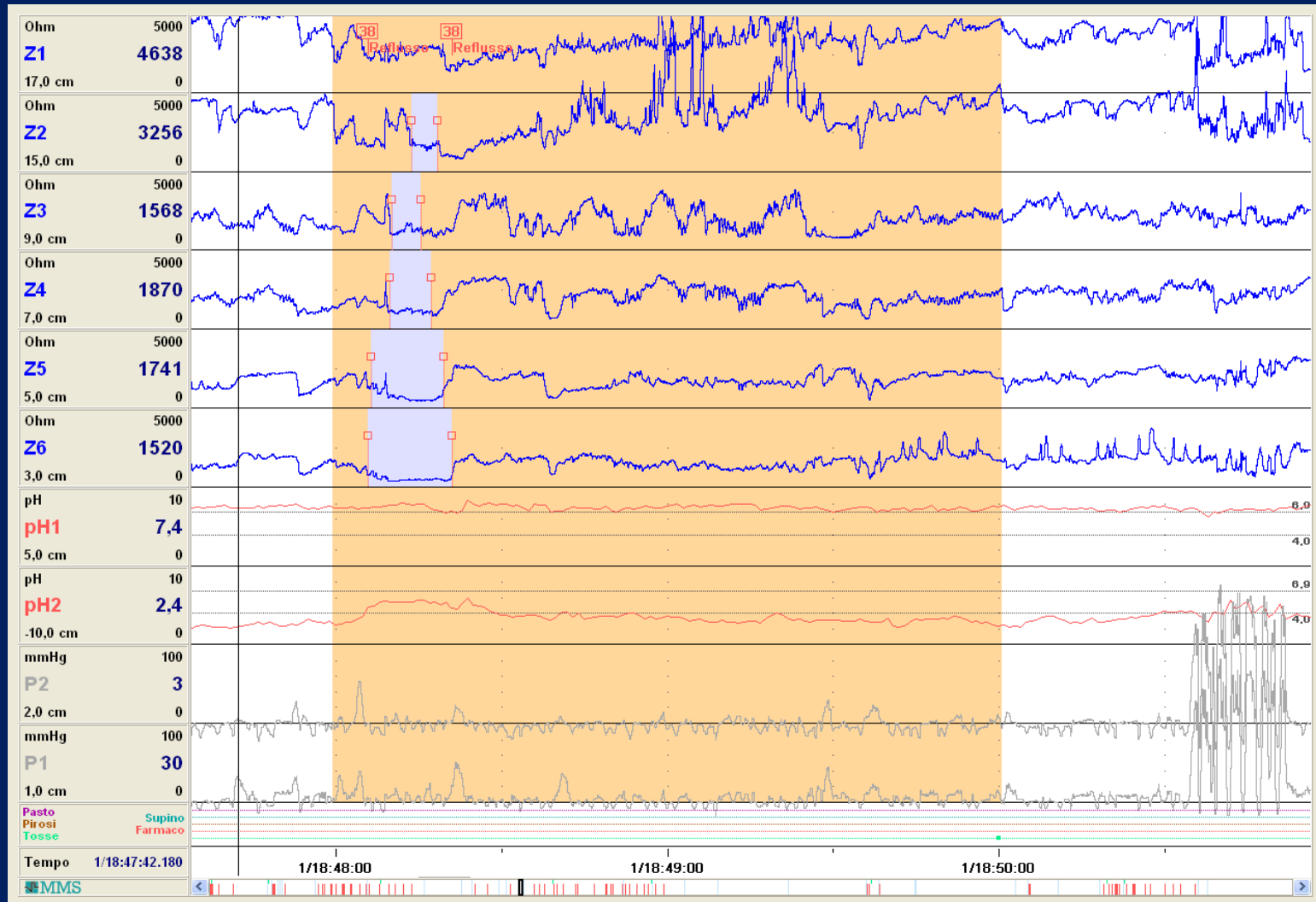
Functional Heartburn



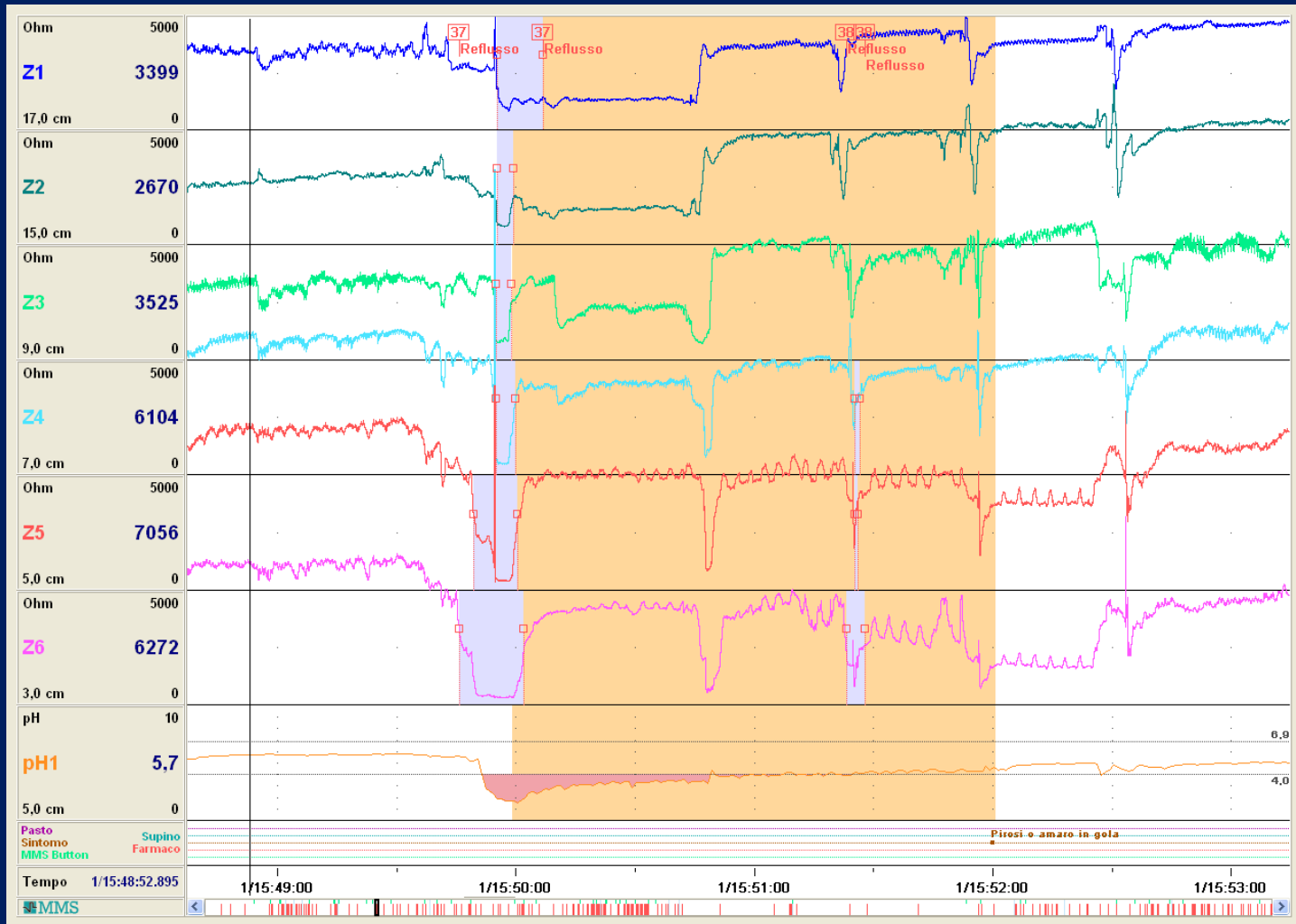
Acid Reflux → Cough



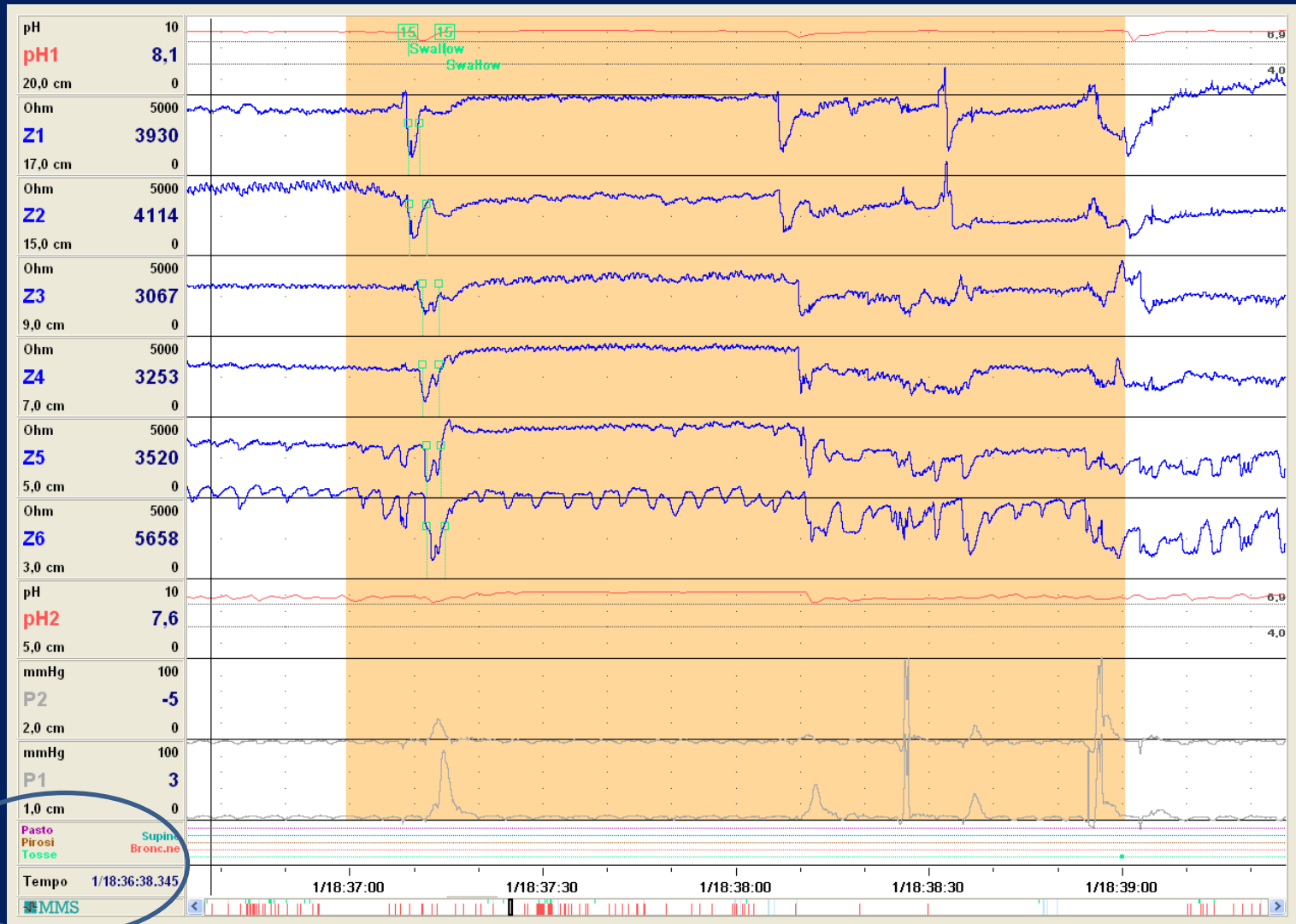
Weakly acid reflux → Cough



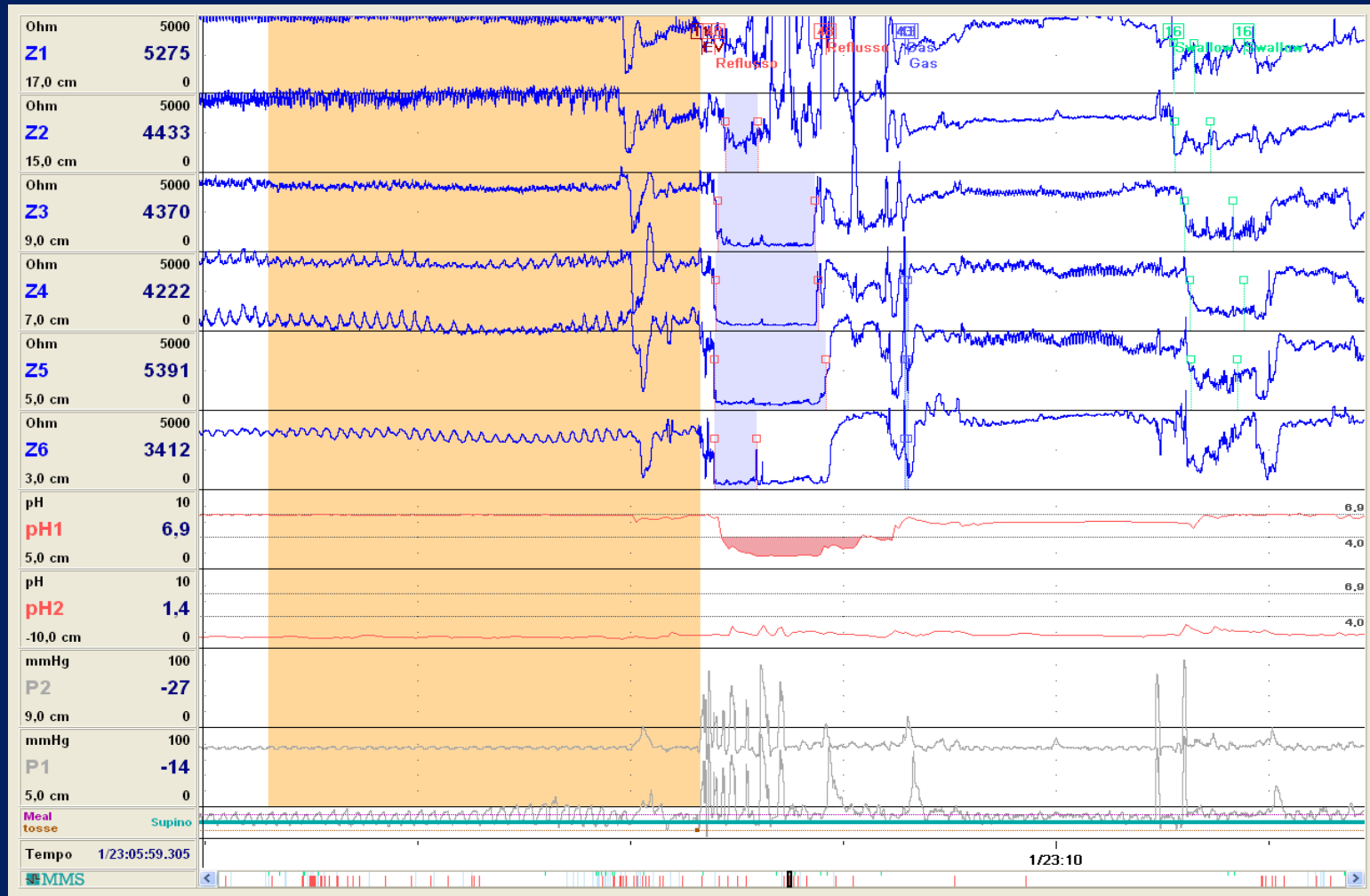
Acid reflux and soare throat



Cough without reflux



Cough → acid reflux



	pH monitoring	MII-pH Monitoring
Acid GER	√	√
Nonacid GER		√
Acid re-reflux		√
Liquid, Gas, Mixed Reflux		√
Proximal migration of refluxate	1 or 2 levels	6 levels
Chemical clearance	√	√
Post-prandial GER	50%	100%
Symptom association to acid GER	√	√
Symptom association to non acid GER		√

Limitations of intraluminal electrical impedance

- Invasive technique
- Low patient's compliance
- Technical failure of the measuring system
- Existence of severe esophageal motor abnormalities
- Inability to detect the volume of air or liquid
- Inability to distinguish between bile reflux or reflux of other non-acidic gastric contents as food material
- Validation of automated software-aided analysis is not yet completely established

Subcategorization of NERD patients by pH-MII

SUB-CLASSIFICATION OF NERD

by pH-impedance testing

Savarino E et al, AJG 2008

True NERD

Abnormal pH-testing
42%

GOOD RESPONSE TO PPI THERAPY

True Functional Heartburn

Normal pH-testing and Negative
Symptom Association
26%

NO RESPONSE TO PPI THERAPY

Hypersensitive Esophagus to Acid

Normal pH-testing and Positive
Symptom Association
15-20%

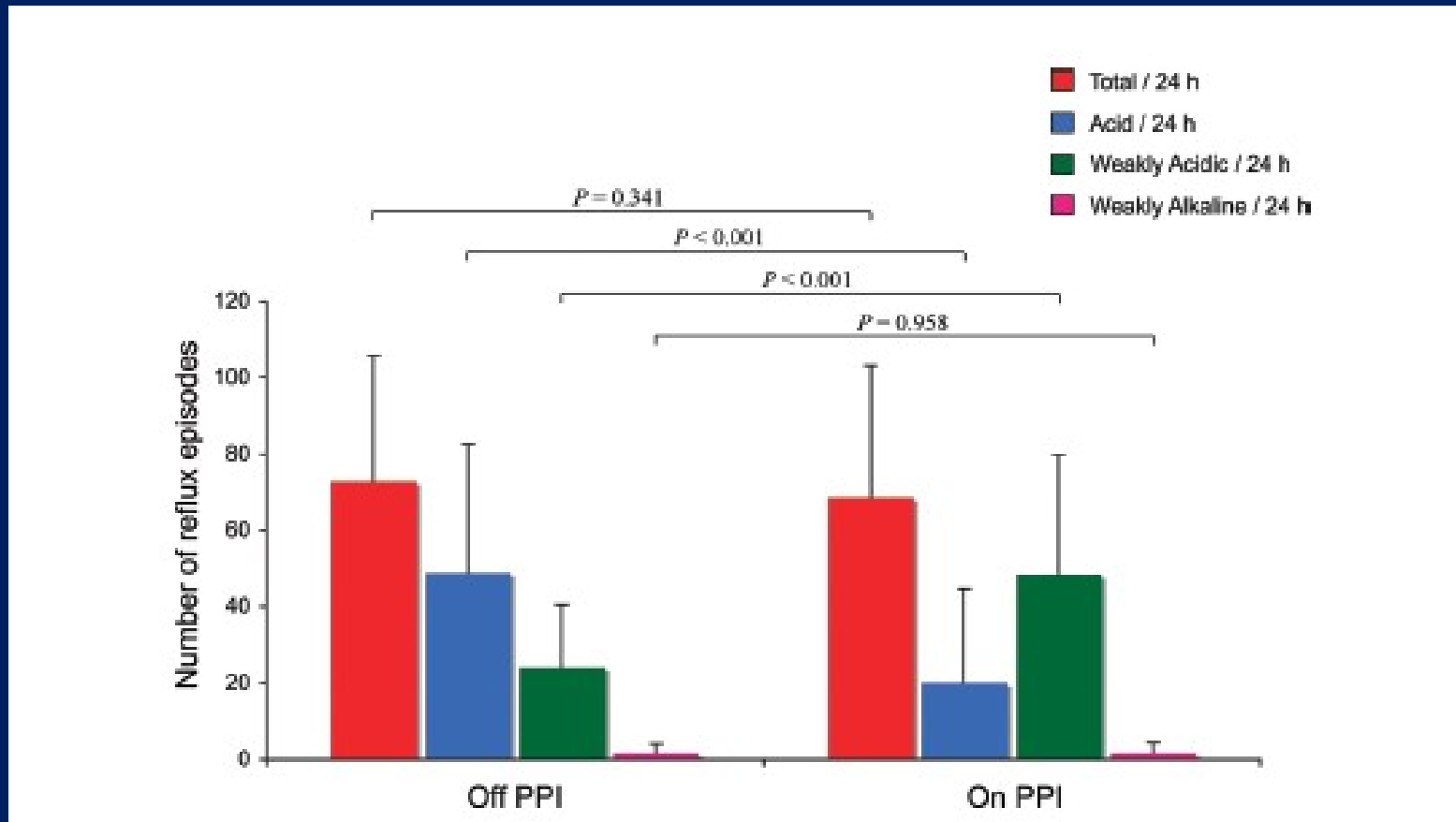
POSSIBLE RESPONSE TO PPI THERAPY

Hypersensitive Esophagus to NonAcid

Normal pH-testing and Positive
Symptom Association
12-17%

NO RESPONSE TO PPI THERAPY

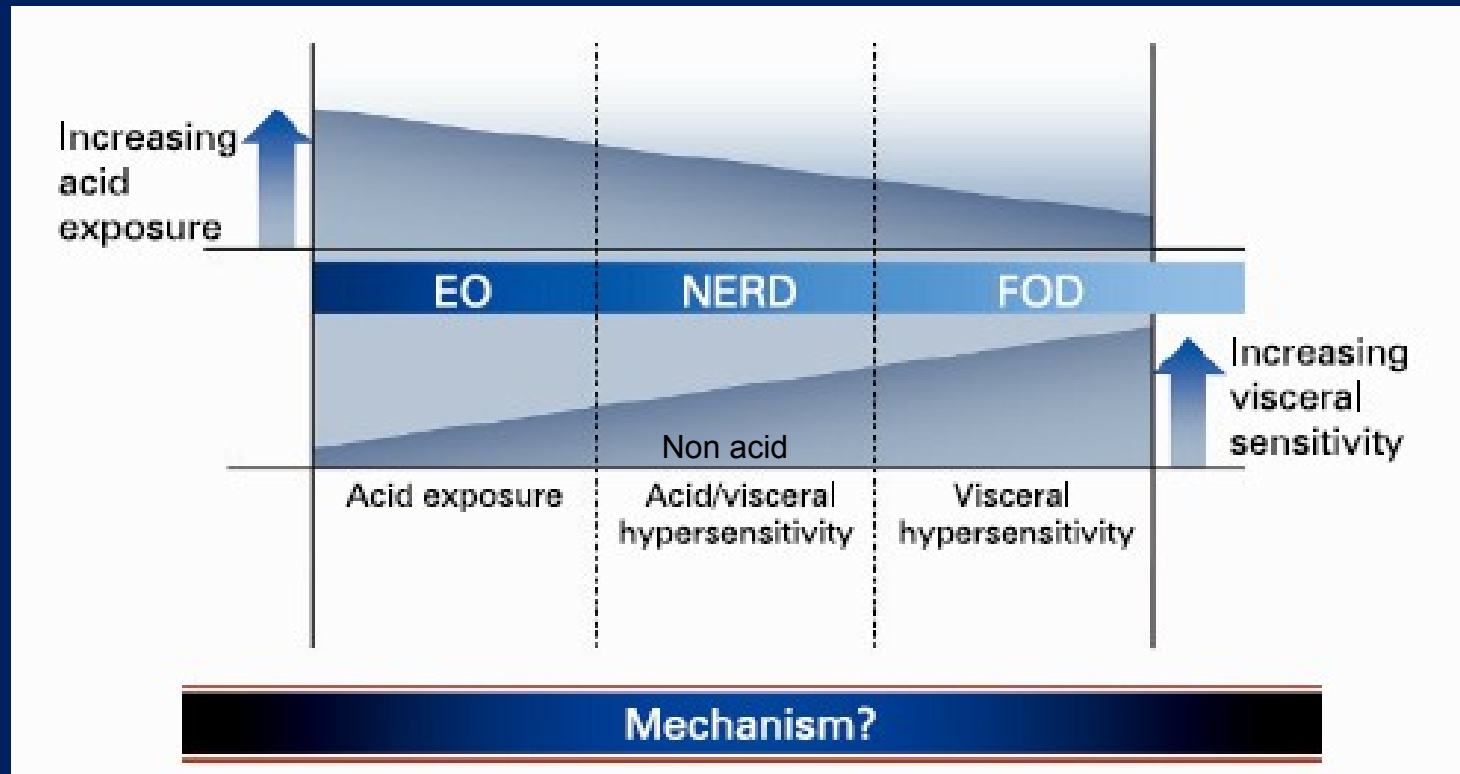
24-hour reflux episodes off and on PPI therapy in GERD patients



Hemmink et al, Am J Gastroenterol, 2008

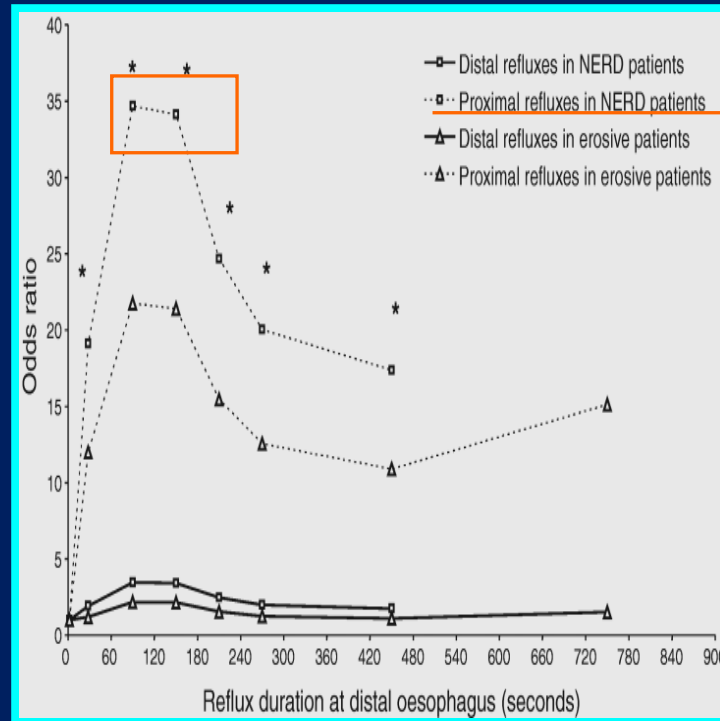
Mechanisms responsible for symptoms in:

- NERD:**
- Hypersensitivity to weakly acidic refluxate
 - Esophageal distension by increased reflux volume

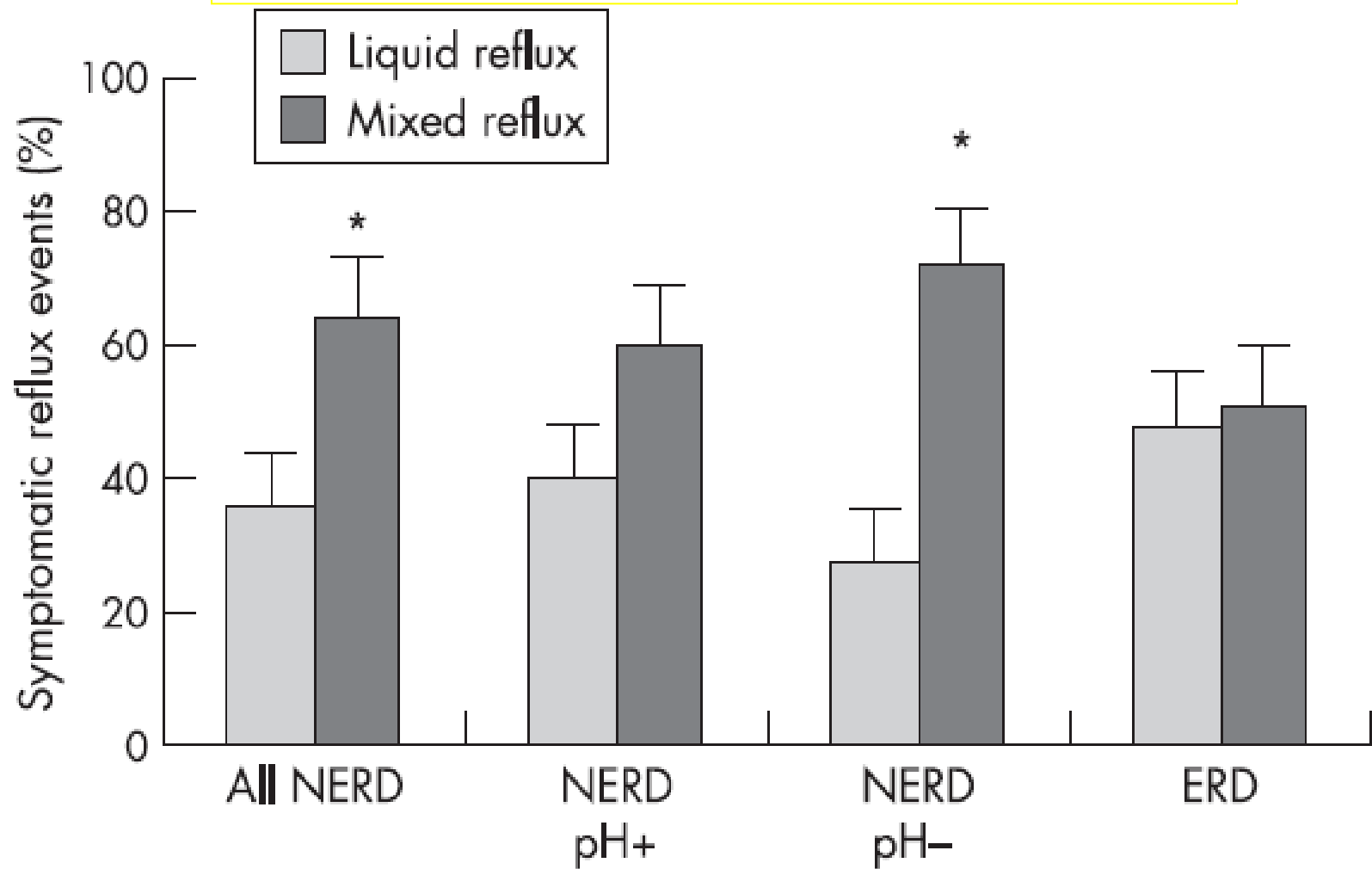


FH: Esophageal hypersensitivity to chemical, mechanical, and electrical stimuli

Possibili meccanismi: ipersensibilità al reflusso acido e debolmente acido in esofago prossimale dei pz con NERD vs ERD



Gas in refluxate enhances reflux perception



Conclusions I

- NERD is an umbrella concept which underlies heterogeneous subgroups of patients without endoscopically visible lesions of esophageal mucosa
- On pH-impedance testing, they can be divided into:
 - subgroup with normal esophageal acid exposure (pH-)
 - subgroup with abnormal esophageal acid exposure (pH+)
- The subgroup with pH- includes pts with:
 - hypersensitive esophagus to acid reflux
 - hypersensitive esophagus non-acid reflux or
 - to both of them

Conclusions II

- The remaining cases with normal esophageal acid exposure and negative symptom index for all reflux types can be classified as patients with **functional heartburn**.

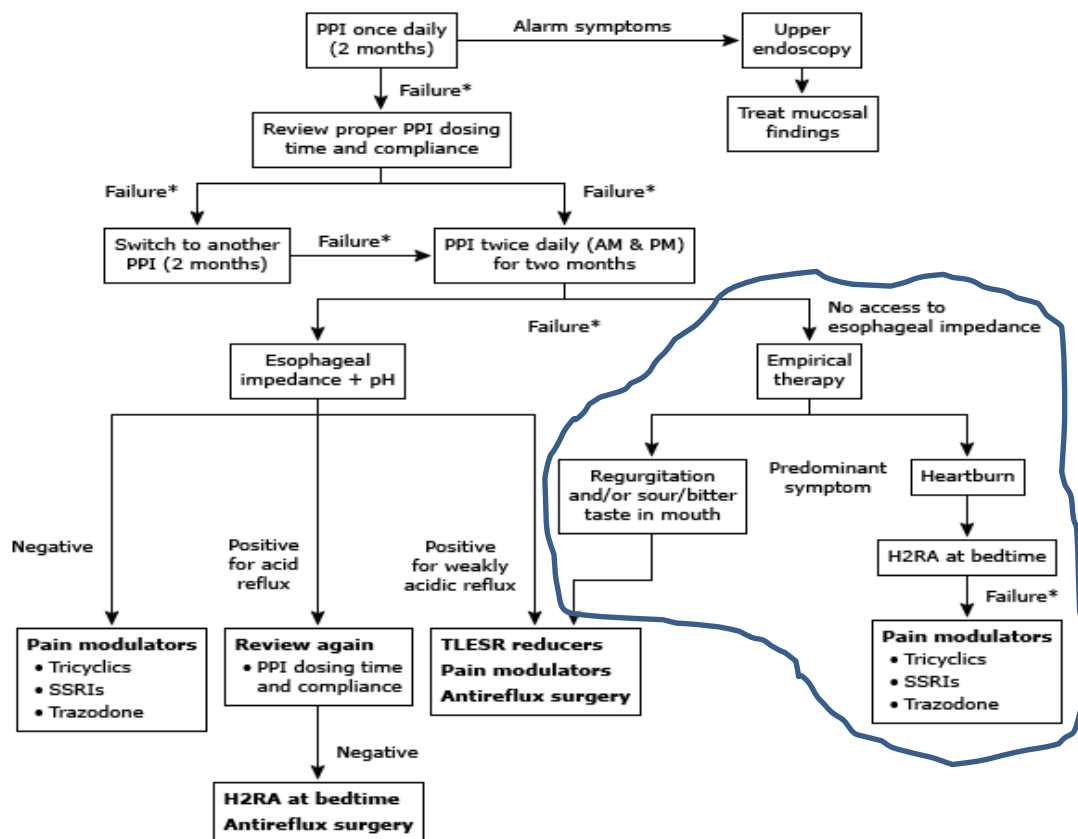
According to Rome III criteria, these patients don't respond to an adequate PPI therapeutic trial.

- Patients with **functional heartburn** are no more considered within the realm of GERD and must be treated with drugs other than acid lowering agents.

Who are you?



Management algorithm of GERD patient who failed PPI once daily





Grazie per l'attenzione

BE prevalence

- Adult general population: 1,6-5,6%

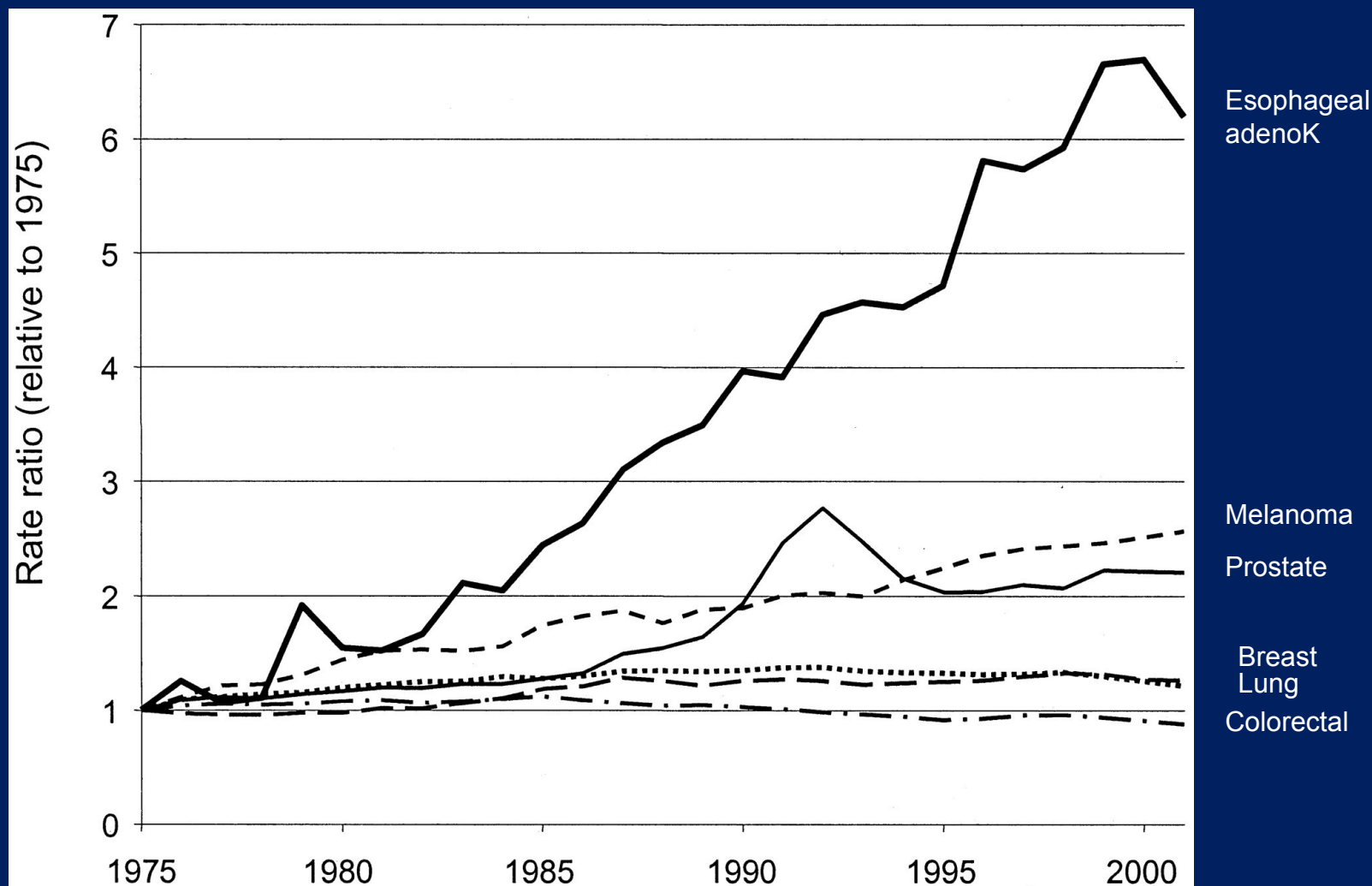
Hayech TJ et al. Dis Esophagus. 2010; 23:451-7

- Adult GERD patients: 10%

Westhoff B et al. Gastrointest Endosc 2005; 61; 226-31

Relative change in incidence of esophageal adenocarcinoma and other malignancies (1975–2001)

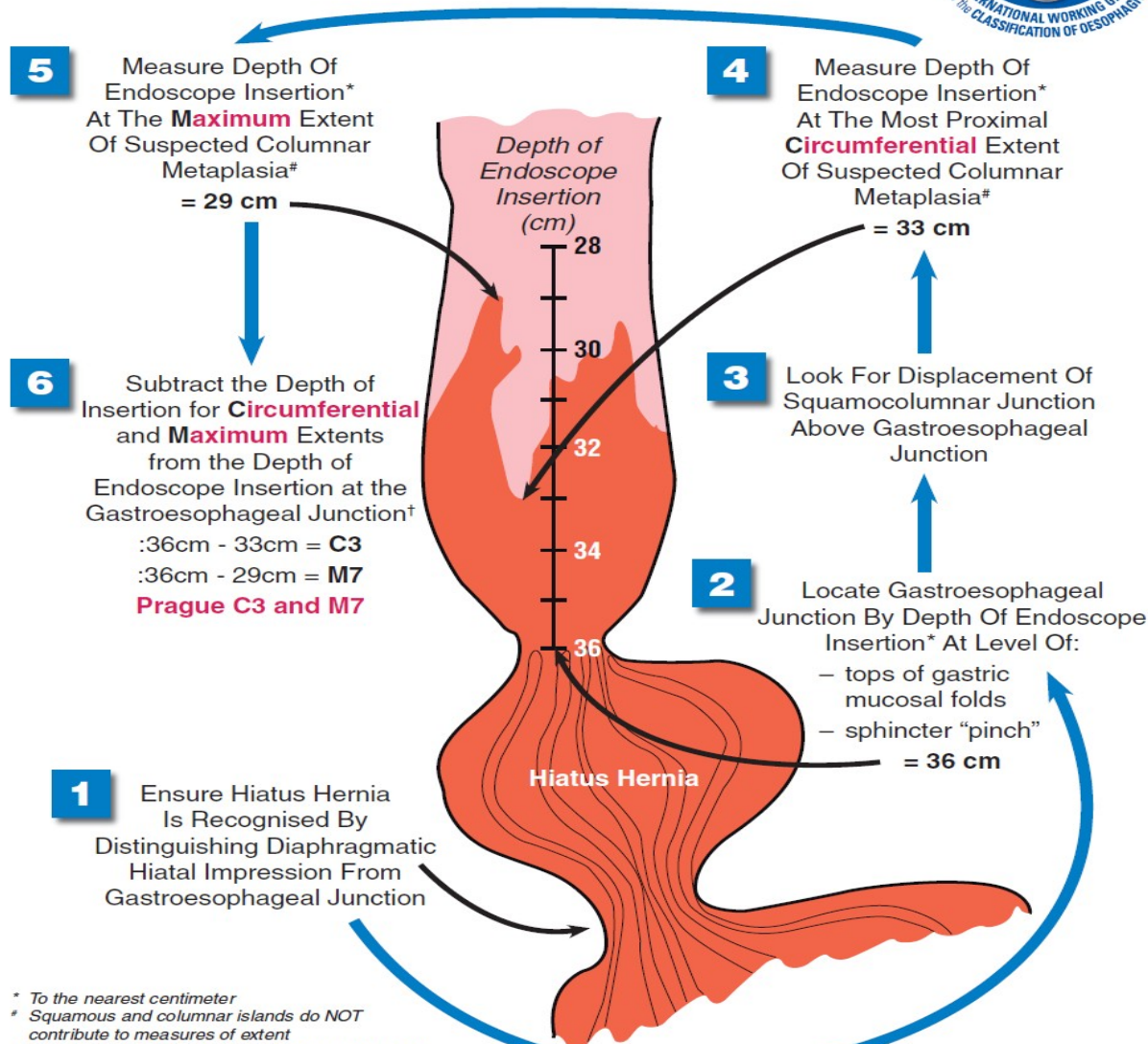
The absolute incidence increased ~ sixfold, from 4 in 1973–5 to 24 per million in 2001



PRAGUE CRITERIA

For Endoscopically Suspected Esophageal Columnar Metaplasia/Barrett's Esophagus

Developed by the Barrett's Oesophagus Subgroup of the International Working Group for the Classification of Reflux Oesophagitis (IWGCO)



* To the nearest centimeter

Squamous and columnar islands do NOT contribute to measures of extent

† To the nearest centimeter, except when areas of columnar metaplasia are estimated to be less than 1 cm: report this as <1 cm



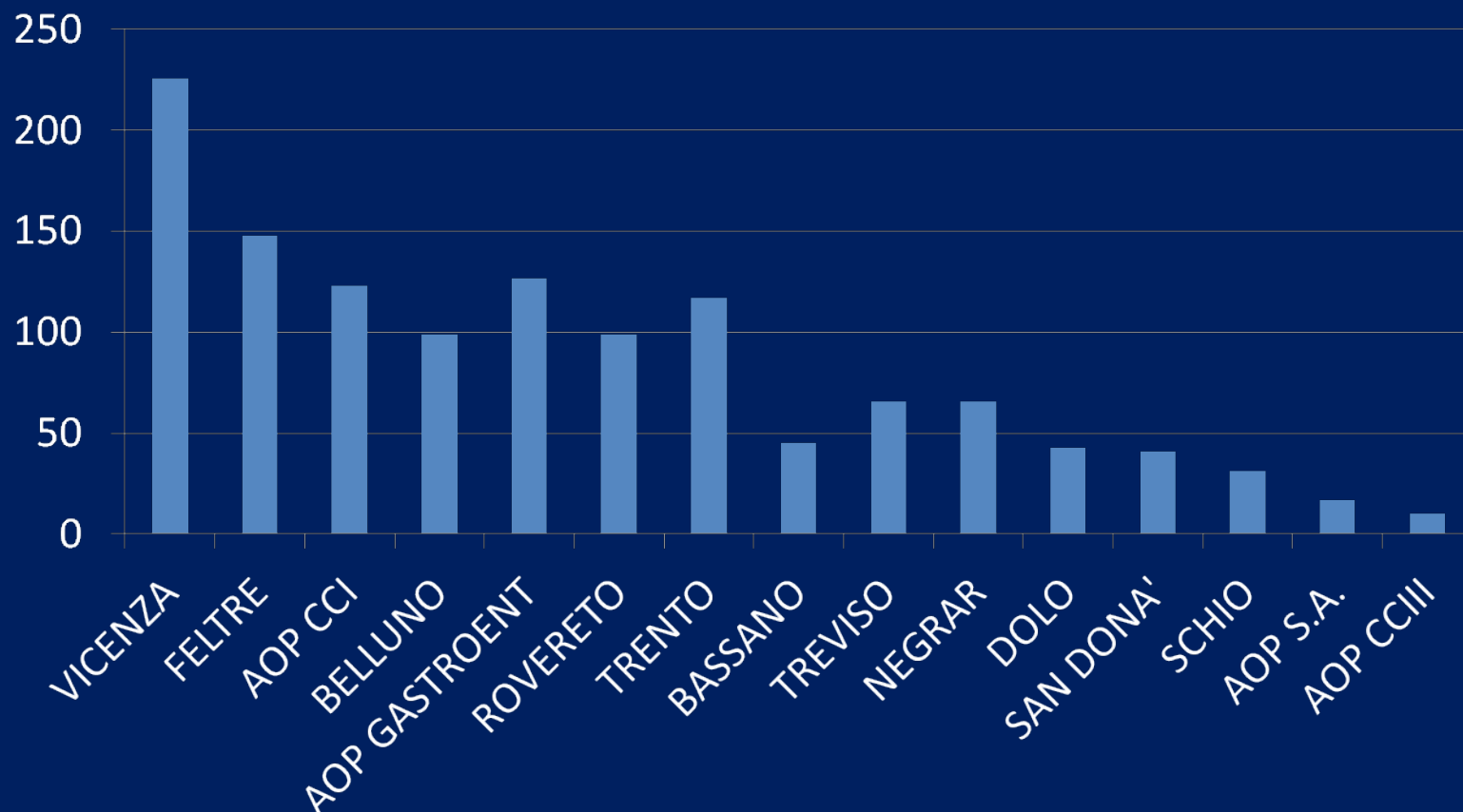
Esofago di Barrett & Rischio di Adenocarcinoma (E.B.R.A.)

Coordinatori scientifici Giovanni Zaninotto e Massimo Rugge

IL REGISTRO NEL TRIVENETO



PAZIENTI EBRA ARRUOLATI (2004-11): 1344



Barrett's Esophagus and Adenocarcinoma Risk: the Experience of the North-Eastern Italian Registry (EBRA)

From the *Esofago di Barrett e Rischio di Adenocarcinoma* (EBRA) Study Group

List of Authors (EBRA study group):

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Audit: Paola Parente, M.D.(Dept of Pathology, Casa Sollievo della Sofferenza, S.Giovanni Rotondo) and Lisa Zanatta² , M.D.

Biostatistician: Francesco Cavallin, MS, Veneto Institute of Oncology [IOV-IRCCS], Padova

Patients' clinical assessment and enrollment in the Registry: Bastianello Germanà, M.D., Ettore Macri, M.D., Ermenegildo Galliani M.D, Paolo Iuzzolino M.D (Dept of Gastroenterology and Pathology Belluno Hospital), Francesco Ferrara M.D, Renato Marin M.D, Emiliano Nisi M.D., Gaetano Iaderosa M.D., (Dept of Gastroenterology and Dept of Pathology, Dolo Hospital), Michele DeBoni M.D., Angelo Bellumat M.D., Flavio Valiante M.D., Georgeta Florea M.D., Duilio Dalla Libera M.D., (Dept of Gastroenterology and Pathology, Feltre Hospital), Marco Benini M.D., Laura Bertasi M.D., (Dept of Gastroenterology and Dept. of Pathology, Negrar Hospital), Alberto Meggio M.D., Maria G. Zorzi M.D., (Dept of Gastroenterology and Dept of Pathology) Rovereto Hospital; Giovanni Depretis M.D., Gianni Miori M.D., Luca Morelli M.D., (Dept of Gastroenterology and Dept of Pathology, S.Chiara Hospital Trento); Giovanni Cataudella M.D., Emanuele D'Amore M.D., Ilaria Franceschetti M.D., Loredana Bozzola M.D., (Dept of Gastroenterology and Dept of Pathology, S.Bortolo Hospital, Vicenza), Elisabetta Paternello M.D., Cristina Antonini M.D., (Dept of Surgery and Dept of Pathology, S.Donà Hospital), Francesco Di Mario M.D., Nadia Dal Bò M.D., Alberto Furlanetto M.D., (Dept of Gastroenterology and Dept of Pathology, Cà Foncello Hospital, Treviso), Lorenzo Norberto M.D., Lino Polese M.D., Silvia Iommarini M.D., Fabio Farinati M.D., (Dept of Surgery -Gastroenterology and Dept of Pathology, University of Padova Hospital), Giorgio Battaglia, M.D., Stefano Realdon M.D., (Veneto Institute of Oncology [IOV-IRCCS], Padova); Ennio Guido M.D., (Dept of Gastroenterology, S.Antonio Hospital, Padova), Gaetano Mastropaolo M.D., Daniela Canova M.D., Antonello Guerini M.D., (Dept of Gastroenterology and Dept of Pathology) Bassano Hospital); Lisa Franceschi M.D., Maurizio Zirillo M.D., (Dept of Gastroenterology and Dept of Pathology, S. Camillo Hospital, Schio)

Ann Surg; novembre 2012

Table 3.**Incidence and timing of progression to HG-IEN/BAc, stratified by presence of LG-IEN and length of BE segment (SSBE vs LSBE)**

	N.	Follow-up p/y	Progression to EAC/HG-NiN	Incidence EAC / HG-NiN (p/ys)	Time to progression in months: median (IQR)
All patients	841	3058	22	0.72 %	40.2 (26.9-50.4)
IM without NiN	777	2837	15	0.53%	40.5 (23.3 – 57.3)
IM without NiN - SSBE	454	1628	8	0.49%	42.7 (35.9-46.9)
IM without NiN - LSBE	323	1209	7	0.58%	33.8 (24.7-44.3)
LG NiN	64	221	7	3.17%	55.1 (20.0-66.0)
LG NiN -SSBE	34	103	3	2.91%	21.0 (16.9-55.1)
LG NiN- LSBE	30	118	4	3.39%	62.9 (39.9-69.1)

BE radiofrequency ablation by Halo system 360 -90

