Repeated surgical or endoscopic myotomy for dysphagia in recurrent achalasia

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Aim: Surgical myotomy (SM) of the lower esophageal sphincter (LES) has a five year success rate on dysphagia of about 91%. Recent reports seem to indicate that endoscopic peroral myotomy (POEM) can give similar short-term successful results on the control of dysphagia. Some patient, however, can experience either persistent or recurrent dysphagia after myotomy. The aim of this study is to evaluate our experience in redo myotomy for recurrent dysphagia in patients with achalasia.
Methods: In the period March 1996 – February 2015, 232 myotomies for primary or recurrent achalasia were performed in our Center: there were 31 POEM and 201 surgical myotomies. Thirteen patients (5.6%) had a previous myotomy and were operated on for recurrent symptoms: nine patients had a surgical redo myotomy and 4 patients had an endoscopic redo myotomy.
Results: The patients presented themselves after a mean of 13.4 years after previous myotomy (range 0.7–33). Previous myotomy was performed through abdominal approach in 11 patients (7 laparoscopic), thoracic in one and endoscopic in one. Mean preoperative Eckardt score was 5.4 (range 0–9). Among the nine patients having a surgical myotomy, eight were completed laparoscopically; in this group there were three esophageal perforations, which were immediately repaired. Mean duration of surgery was 114 min (range 56–170) in the surgical group and 78 (range 60–112) in the POEM group. There were no postoperative complications in both groups. Mean postoperative stay was 4 days (range 2–9) in the surgical group and 2.5 days (range 2–3) in the POEM group. In the surgical group, Eckardt score was <3 in seven out of nine patients after a mean follow-up of 19 months (range 1–49); it was <3 in all four patients in the POEM group after a mean follow-up of 5 months (range 1–11).
Conclusions: Redo myotomy for recurrent dysphagia in patients with achalasia is effective in more than 80% of patients. Preliminary results with PEOM seem to indicate that the technique can be safely applied in patients with previous surgical myotomy.

Esophageal perforation after endoscopic pneumatic dilation: laparoscopic repair

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Introduction: Pneumatic dilation of the cardia (PD) represents a standard treatment for several motors disorders of the esophagus. Recent randomized trials have demonstrated that, in the treatment of achalasia, the long-term results of PD in terms of dysphagia control are comparable to those obtained by surgical myotomy. The main disadvantages of PD are the frequent need to repeat the treatment in order to obtain effective and durable results, and the risk of esophageal perforation of the technique. In order to have a low risk of perforation, PD should start with 30-mm diameter balloon. Notwithstanding, the risk of esophageal perforation after PD is reported to be around 1 and 4.3%, with a related mortality rate of 1–20%.
The treatment of esophageal perforation after PD can be conservative, endoscopic, or surgical according to various parameters of severity of the perforation.
Case Report: We report the case of a 64-year-old lady, who was submitted to PD with a 30 mm Rigiflex balloon for a motor disorder of the esophagus causing severe dysphagia, occasionally associated to thoracic pain. Radiology was typical for achalasia but HR manometry showed a lower esophageal sphincter basal and residual pressure at the higher limits of normal range. At postdilation endoscopic control, a precardial mucosal perforation of several centimeters was detected. A CT scan showed a pneumomediastinum and an extraluminal leakage of contrast medium through a lesion of the posterior esophageal wall, several centimeters proximal to the esophagogastric junction. The patient was suffering, tachipnoic and tachicardic. Immediate surgery was planned.
Surgery (video) consisted in laparoscopic repair of the esophageal perforation. The operation was completed with an anterior myotomy and a partial posterior antireflux repair. Postoperative course was uneventful and the patient resumed a soft diet on the third postoperative day after a radiological gastrografin swallow on 2nd postoperative day. Four months after surgery the patient is asymptomatic.
Conclusion: Early surgery is a safe and effective treatment in case of severe esophageal perforation after PD. Laparoscopy is a good access for this treatment and its results are dependent on a prompt intervention.

The role of integrated relaxation pressure in achalasia and its modification after heller myotomy

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Background: A new classification for the diagnosis of primary esophageal motility abnormalities by means of High-Resolution Manometry (HRM) has been recently proposed and a new parameter, the Integrated Relaxation Pressure (IRP), has been included for the assessment of esophagogastric junction (EGJ) relaxation. Indeed, the diagnosis of achalasia is established by HRM on the basis of an IRP >15 mmHg and absence of normal peristalsis in the esophageal body. The aims of this study were: (i) to investigate the correlation of IRP values with the diagnosis of achalasia, the demographics and clinical findings in a group of consecutive well-defined achalasia patients, (ii) to assess the effect of Heller myotomy on IRP.

Methods: We evaluated all consecutive patients who underwent laparoscopic Heller myotomy as first treatment from 2009 to 2014 and had a HRM evaluation before and after surgery. Patients who had already been treated for achalasia (with Heller myotomy, endoscopic treatment) were excluded from the study. The diagnosis of primary achalasia was established by esophageal manometry on the basis of accepted esophageal motility characteristics. Symptoms were collected and scored using a detailed questionnaire for dysphagia, food-regurgitation, and chest pain; barium swallow, endoscopy, HRM were performed, before and 6 months after surgical treatment. Treatment failure was defined as a postoperative symptom score >10th percentile of the preoperative score (i.e., >10).
Results: 139 consecutive achalasia patients (M : F = 72 : 67) represented the study population. All the patients had 100% simultaneous waves but 11 had a IRP <15 mmHg. According to the HRM classification, patients were classified as having: 58 (42.3%) type I, 63 (46%) type II and 16 (11.7%) type III.
At univariate analysis IRP was correlated with the gender, the basal and resting lower esophageal sphincter (LES) pressure, and the dysphagia score.
All the patients had absence of normal peristalsis, but 11 (10.9%) had an IRP <15 mmHg. All these patients had a barium swallow showing a grade I disease.
At a median follow-up of 24 months, the symptom score was significantly lower after surgery (median preoperative score 18 [IQR 11–20] *vs* median postoperative score 0 [IQR 0–3]; $p < 0.0001$). The resting LES pressure (median preoperatively 27 [IQR 19–36] *vs* median postoperatively 11 [IQR 8–14]; $p < 0.001$) and IRP (median preoperatively 27.4 [IQR 20.4–35] *vs* median postoperatively 7.1 [IQR: 4.4–9.8]; $p < 0.001$). The failures of surgical treatment were 7 (5%).
Conclusion: This is the first study evaluating the role of IRP in achalasia and its modifications after myotomy. An increased preoperative IRP directly correlates with severity of dysphagia in achalasia patients. IRP is reduced to normal values by Heller myotomy. Moreover, the occurrence of an IRP <15 mmHg in more than 10% of patients despite a clinical/radiological/endoscopic diagnosis of achalasia, requires caution in considering this parameter as a discriminating condition in the manometric diagnosis of the disease.

Table

	IRP	*p*-value
Sex		
M	25.1 (17.3–31.1)	**0.01**
F	29.0 (22.8–37.9)	
Age*	−0.12	0.25
Manometric pattern		
I	25.9 (18.7–31.3)	0.24
II	29.9 (22.3–35.5)	
III	24.7 (17.2–44.3)	
Esophageal diameter*	−0.03	0.79
LES basal pressure*	0.56	**<0.001**
LES total length	0.17	0.08
LES abdominal length	0.15	0.14
LES residual pressure*	0.86	**<0.001**
Dysphagia score*	0.21	**0.04**
Symptoms score*	0.14	0.17

*Spearman's coefficient.

Clinical and high-resolution manometry data support the hypothesis that proton pump inhibitor-responsive esophageal eosinophilia represents a GERD-related phenomenon

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Introduction & Aim: It is unclear if Proton Pump Inhibitor-response esophageal eosinophilia (PPI-REE) is a gastro-esophageal reflux disease (GERD)-related phenomenon, a subtype of Eosinophilic esophagitis (EoE), or a completely unique entity. High-resolution manometry (HRM) is a novel technique that has been recently shown to provide new insights on GERD pathogenesis. In particular, esophagogastric junction (EGJ) morphology different from type I and weak peristalsis have been strongly associated with GERD. We aimed to compare HRM features of patients with EoE and PPI-REE.
Methods: Consecutive patients with EoE (>15 eos/hpf on esophageal biopsies) and PPI-REE (<15 eos/hpf and a 50% decrease from baseline) diagnosed after twice-daily PPI for at least 8 weeks were enrolled. Patients underwent HRM to assess the esophago-gastric junction (EGJ) and esophageal peristalsis. Tracings were analyzed based on Chicago Classification vers. II and, furthermore, each EGJ was classified as: Type I, no separation between the Lower Esophageal Sphincter and the Crural Diaphragm; Type II, minimal separation (>1 and <2 cm); Type III, >2 cm of separation.
Results: Thirty-one patients had EoE [24M/7F; mean age 28], whereas 10 patients had PPI-REE [9M/1F; mean age 38]. The two cohorts had similar dysphagia for solids ($p = 0.6979$), bolus impaction ($p = 1.000$) and chest pain ($p = 1.000$), but different heartburn (26% *vs* 60%, $p = 0.0485$) and regurgitation (16% *vs* 50%, $p = 0.0446$). Endoscopic features had the same frequency. At HRM testing, EoE patients had higher mean integrated relaxation pressure [9 *vs* 6, $p = 0.0616$] and LES basal pressure [26 *vs* 17, $p = 0.0388$], but similar mean distal contraction integral [$p = 0.5613$] compared to patients with PPI-REE. Type II and III EGJs were less common in EoE than in PPI-REE patients (9% *vs* 50%, $p = 0.0129$). Manometric diagnoses were similar between EoE and PPI-REE: weak peristalsis (16% *vs* 40%, $p = 0.2221$), absent peristalsis (3% *vs* 10%, $p = 1.0000$) and distal esophageal spasm (3% *vs* 0%, $p = 1.0000$).
Conclusions: Typical reflux symptoms and HRM features GERD-related are more common in patients with PPI-REE than in patients with EoE. These data support the hypothesis that PPI-REE may represent a GERD-related phenomenon rather than a subtype of EoE.

Clinical and impedance-pH patterns predict response to proton pump inhibitors in patients with non-cardiac chest pain

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Background & Aim: Gastroesophageal reflux disease (GERD) is the most common cause of non-cardiac chest pain (NCCP). Previous studies showed that proton pump inhibitors (PPIs) are less effective in relieving NCCP than heartburn, but predictors of PPIs response in NCCP patients have not been investigated yet. We aimed to determine whether any symptom profile or reflux pattern at impedance-pH monitoring was associated with PPIs refractoriness.
Methods: Consecutive patients with NCCP were prospectively enrolled. Demographics and clinical data were collected. All patients underwent upper endoscopy and, within 3 days impedance-pH testing off-PPI therapy. We measured distal esophageal acid exposure time (AET), characteristics of reflux episodes (acid/weakly acidic) and symptom-reflux association using both symptom association probability (SAP+ if ≥95%) and symptom index (SI+ if ≥50%). Patients were classified as PPI-responders (PPI-R), if they had a symptom relief >50% from baseline or if they had fewer than 1 day of mild NCCP per week while receiving a double dose of PPI treatment for at least 8 weeks.
Results: One hundred and twenty-two NCCP patients (56F/66M; mean age 47; 100 PPI-NR/22 PPI-Responders) were included. At univariate analysis, PPI-R presented more frequently erosive esophagitis and hiatal hernia ($p = 0.057$ and $p = 0.03$, respectively), typical (heartburn and/or regurgitation) or atypical (cough and/or asthma) reflux symptoms ($p = 0.003$) and reported less often dyspepsia ($p = 0.02$) compared to PPI-NR. Furthermore, PPI-R had more frequently an abnormal AET (45% *vs* 21%, $p = 0.02$), a greater mean AET (9.9 [2.9–48] *vs* 1.15 [0.6–15], $p < 0.01$), a higher mean number of total (80 [16–177] *vs* 47 [10–228], $p = 0.0037$), weakly acidic (34.5 [7–101] *vs* 24 [2–145], $p = 0.031$) and acidic (44 [6–91] *vs* 24 [8–98], $p = 0.011$) reflux episodes compared to PPI-NR. No differences were found between PPI-r and PPI-NR in terms of SI and SAP positivity for acid, weakly acid or both kind of reflux (data not shown). At multivariate analysis, the factors associated with PPIs refractoriness were the lack of concomitant reflux symptoms, presence of functional dyspepsia, a normal AET and a reduced number of reflux episodes ($p < 0.01$).
Conclusion: Our data show that symptom profile and reflux features detected at impedance-pH are associated with lack of response to PPI therapy in patients with NCCP.

Esophagogastric junction morphology predicts a positive impedance-pH test in patients with GERD

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Background: High-resolution manometry (HRM) provides a better representation of the esophagogastric

junction (EGJ) isolating the crural diaphragm (CD) from the lower esophageal sphincter (LES). According to the Chicago Classification (CC), three different EGJ morphologic subtypes can be detected based on the separation between the LES and the CD.
Aim & Methods: We aimed to correlate the different EGJ subtypes with impedance-pH findings in gastro-esophageal reflux disease (GERD) patients. Consecutive patients with heartburn and/or regurgitation were enrolled. All patients underwent a 36-Solid-State HRM with a 5-min baseline recording and 10 single water swallows (5 mL) to evaluate the esophageal peristalsis and EGJ function. Tracings were analyzed based on the CC and each EGJ was classified as: Type I, no separation between the LES and the CD; Type II, minimal separation (>1 and <2 cm); Type III, >2 cm of separation. The patients also underwent impedance-pH testing off-therapy. We measured esophageal acid exposure time (AET), total number of reflux episodes and symptom-reflux association using symptom association probability (SAP+ if ≥95%) and symptom index (SI+ if ≥50%).
Results: We enrolled 130 consecutive patients and identified 46.2% Type I EGJ, 38.5% Type II and 15.4% Type III patients. Type III subjects had a higher number of reflux episodes (61 *vs* 45, $p < 0.03$, *vs* 25, $p < 0.001$), a greater mean AET (12.4 *vs* 4.2, $p < 0.02$, *vs* 1.5, $p < 0.001$) and a greater positive symptom association (75% *vs* 72%, $p = 0.732$ *vs* 43.3%, $p < 0.02$) compared to Type II and I patients, respectively. In addition, Type II subjects showed statistically significant (overall $p < 0.01$) increased reflux when compared to Type I patients. Type III and Type II morphologies had a more frequent probability to show a positive MII-pH than Type I (95% *vs* 84% *vs* 50%, $p < 0.001$).
Conclusions: With increasing separation between the LES and CD, from Type I to Type III EGJ, patients had a gradual and significant increase in reflux episodes and esophageal acid exposure. Thus, EGJ morphology may be useful to predict an abnormal impedance-pH testing in patients with GERD.

Molecular abnormalities in the intestinal epithelial barrier of patients with chronic intestinal pseudo-obstruction (CIPO)

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Objective: CIPO is a rare and severe condition characterized by the impairment of gut motility that causes a clinical picture mimicking a mechanical obstruction in the absence of any detectable organic abnormality. Enteric neuromuscular (including interstitial cells of Cajal) changes represent the histopathological correlates explaining symptoms and clinical picture of CIPO, other factors, i.e., intestinal epithelial barrier (IEB) abnormalities, may have a pathogenetic impact. The aim of the present study was to assess the expression of occludin and zonula occludens-1 (ZO-1), two major components of tight junctions (TJs), as surrogate markers of IEB integrity in patients with CIPO.
Methods: A number of $n = 26$ well characterized CIPO pts (15 F; age range: 16–75 years) were studied. Patients ($n = 8$; 3 F, age range: 48–73 years) undergoing elective surgery for uncomplicated neoplastic diseases served as control group. Total mRNA and Total proteins were extracted from all the CIPO and control jejunal full thickness biopsies. The mRNA and protein expression of occludin and ZO- was carried out via q-PCR and WB.
Results: Compared to controls, total occludin protein showed a marked decrease in CIPO pts ($p < 0.05$); also, a tendency to a decreased occludin mRNA expression was found in CIPO *vs* controls. Moreover, occludin oligomers, an index of occludin assembly in rafts TJs, were detected only in 19% of CIPO patients while all controls showed normal oligomerization. ZO-1 protein and mRNA expression did not change in CIPO *vs* controls.
Conclusions: In this study, we showed significant occludin protein assembly which supports IEB changes in patients with severe dysmotility (i.e., CIPO). The abnormal occludin oligomerization indicates TJ dysfunction leading to passage of noxious agents through the intestinal wall and thereby into the circulation of these patients.

Molecular differences underlying chronic constipation *vs* constipated Parkinson disease patients

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Background and Aims: The enteric nervous system (ENS) is the major player controlling gastrointestinal (GI) functions. In addition, the ENS can be a target of a variety of pathological conditions, including Parkinson's disease (PD). PD patients are known to suffer from different GI manifestations, the most common being chronic constipation (CC). CC in PD (PD/CC) remains poorly elucidated and the neurochemical/molecular mechanisms underlying its pathophysiology, compared to conventional CC, are still unknown. We analyzed colonic specimens in three groups of patients: PD/CC, CC and control subjects, focusing to the secretomotor neuron component and glial cells.
Methods: In PD/CC and CC patients, symptoms were evaluated by the Rome III questionnaire a thorough GI functional assessment. Twenty-six PD patients (6F, 20M; age range: 64–85 years), 4 CC patients (4F, age range 36–71 years) and 18 asymptomatic controls (7F, 11M; age range: 44–77 years; screening colonoscopy) were enrolled. Each patient and control underwent colonoscopy and using routine biopsies submucosal plexus was obtained for immunohistochemical and molecular analysis. For quantitative immunohistochemistry a panel of antibodies to mouse monoclonal anti-HuC/D (a pan-neuronal marker; 1 : 50; Invitrogen) and a rabbit polyclonal anti-VIP (a secretomotor neuron marker; VIP-7913; CURE/DDRC, UCLA, 1 : 2500) were used. RT-q PCR was also performed to assess relative expression of VIP mRNA on biopsies from 13 CC/PD patients, 4 CC patients and 12 controls. Western blot analysis was performed in 10 CC/PD patients, 4 CC patients and 4 controls to assess GFAP levels (a glial cell marker; rabbit anti-GFAP antibody, DAKO, 1 : 3000).
Results: There were no significant differences in the number of HuC/D immunoreactive (-IR) neurons/ganglion between CC/PD (4.4 ± 0.9) *vs* CC (4.9 ± 0.7) *vs* controls (4.0 ± 1.3); however, a reduced number of HuC/D/VIP-IR neurons was found in CC/PD (73.3 ± 17.1) *vs* controls (85.8 ± 9.4) ($p < 0.05$), but no significant differences were observed in CC (87.5 ± 5.4) *vs* CC/PD neither *vs* controls. RT-q PCR confirmed a significant reduction in VIP mRNA expression selectively in CC/PD patients *vs* controls ($p < 0.05$); CC group did not show significant differences compared to CC/PD and controls. GFAP protein levels increased in PD/CC patients *vs* CC and controls ($p < 0.05$). GFAP levels did not show differences in CC *vs* controls.
Conclusions: Distinctive molecular signatures appear to characterize PD/CC *vs* CC. Specifically, the decrease in VIP mRNA expression and VIP containing (secretomotor) neurons suggest an altered secretory mechanisms operating in PD/CC, but not in CC patients. The increased GFAP protein levels showed an activation of glial cells, leading to postulate a glia-mediated inflammatory mechanisms in PD/CC.

Esophageal bolus contact time and chemical clearance may differentiate patients with non-erosive reflux disease: an impedance-pH monitoring study

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Aims: Knowledge about esophageal volume clearance/exposure in reflux disease is limited. Our study aimed to assess the role of clearance abnormalities in patients with reflux symptoms. First endpoint was to verify whether an automated or a manual analysis of bolus clearance time (BCT) well identified GERD patients impedance-pH classified. Second endpoint was to compare and correlate BCT, baseline impedance levels (BI) and postreflux swallow-induced peristaltic wave index (PSPW) in non-erosive reflux disease (NERD) patients.
Methods: One hundred and eighteen patients with heartburn and/or regurgitation and normal endoscopy underwent impedance-pH monitoring off-therapy. We evaluated acid exposure time (AET), number of refluxes, BI, PSPW and both automated and manual BCT. Patients were sub-grouped in: pH+/MII+ (both abnormal AET and number of refluxes); pH+/MII- (abnormal AET, normal number of refluxes); pH-/MII+ (normal AET, abnormal number of refluxes); and pH-/MII- (normal AET and number of refluxes) as control group.
Results: BI and PSPW were gradually increased from pH+/MII+, pH+/MII−, pH−/MII+ to pH−/MII−

Table 1 24-h MII-pH parameters detected sub-groups of NERD patients

	pH+/MII+ (32)	pH+/MII− (28)	pH−/MII+ (34)	pH−/MII− (24)	*p*
AET total (%)	8.3±3.7	6.2±2.3	1.8±1	0.4±0.4	0.001
Number of reflux events (*n*)	79±26.8	36.3±9.1	70.2±15.6	24.3±9.6	0.001
Proximal reflux events (*n*)	42.3±26.7	14.4±8.2	29.7±12.2	9.3±4.9	0.001
Baseline impedance values (Ω)	1144.5±422.1	1580.5±861.5	1723.3±434.4	3652.5±888.4	0.001
PSPW index (%)	23.8±2.6	29±2.5	35.2±1.8	77.3±4.9	0.001
SAP positive (*n*)	24/32	20/28	19/34	0/24	N.A.

All values are expressed as mean value ± standard deviation (SD).

Table 2 Spearman correlations between manual BCT (3 and 5 cm) and different MII-pH parameters (baseline impedance values; AET; PSPW index)

	Baseline impedance	AET total	PSPW index
Manual BCT 3 cm			
Correlation coefficient (*r*)	−0.853	0.851	−0.904
p	0.0001	0.0001	0.0001
Manual BCT 5 cm			
Correlation coefficient (*r*)	−0.852	0.858	−0.889
p	0.0001	0.0001	0.0001

Correlation is significant at the 0.01 level (two-tailed). Baseline impedance (Ohms); AET (%).

($p < 0.001$). The percentage of patients correctly classified using automated BCT corresponds to half the percentage using manual BCT (36%, 78%, 72%, respectively for automated BCT, and manual BCT at 3 and 5 cm). Manual BCT values were progressively lower from pH+/MII+, pH+/MII−, pH−/MII+ to pH−/MII− both at 3 cm and at 5 cm ($p < 0.001$). We also found an inverse correlation between manual BCT and both BI and PSPW, and a direct correlation between manual BCT and AET ($p < 0.0001$).
Conclusions: BI levels, PSPW and manual BCT could improve the distinction among different sub-groups of NERD patients.

IBS and low-fodmaps diet in IBS: effects on symptoms and micronutrients intake

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Background: Diets with reduced content of substances poorly-incompletely absorbed (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols-FODMAPs), have been shown to ameliorate symptoms in patients with irritable bowel syndrome (IBS). However, the influence of local diet habits on efficacy and potential effects on adequate nutrient intake are unclear.
Methods: 29 IBS pts (21–67 years, 24 females) were enrolled in the study while on their usual diet and underwent nutritional evaluation and counseling every 3 weeks: T0 instruction for low-FODMAPs diet, symptoms and quality of life evaluation; T1, instruction for reinserting previously withdrawn food, symptoms and quality of life evaluation; T2 symptoms and quality of life evaluation. During the entire duration of the study patients were required to complete an alimentary diary.
Results: 69% of patients completed the protocol, 9 (31%) interrupted the study (3 because of symptoms worsening, 2 absence of beneficial effect, 3 inadequate compliance). Low-FODMAPS diet was well-tolerated by the majority of patients, although was judged frustrating and boring. During low-FODMAPS diet patients reported significant improvement of intestinal and extraintestinal symptoms, except for constipation both after 3 weeks diet and after dietician-guided food reintroduction.

Low-FODMAPs diets was also accompanied by ameliorations in quality of life evaluation in both physical and mental environment (respectively [PCS-12 T0 43.5, T1 48.2, T2 47.7; MCS-12 T0 39.3,T1 45.4,T2 48.9]).

Symptoms	T0	T1	T2	*P* T1 *vs* T0	*P* T2 *vs* T1	*P* T2 *vs* T0
Abd sympt	5.9 ± 2.2	3.2 ± 2.5	3.4 ± 1.8	0.001	0.181	0.004
Discomfort	7.7 ± 1.4	3.3 ± 2.6	4.0 ± 1.9	0.000	0.012	0.000
Pain	5.8 ± 2.9	2.8 ± 2.6	3.3 ± 2.2	0.001	0.046	0.001
Bloating	7.1 ± 1.7	3.3 ± 2.3	3.9 ± 1.9	0.000	0.013	0.000
Diarrhea	4.7 ± 3.2	2.1 ± 2.2	2.0 ± 2.2	0.003	0.301	0.000
Urinary	2.0 ± 2.2	0.7 ± 1.3	1.0 ± 1.9	0.003	0.396	0.036
Fatigue	5.6 ± 3.1	3.6 ± 3.2	2.9 ± 2.1	0.003	0.722	0.001
Headache	3.9 ± 3.0	2.0 ± 2.2	2.0 ± 1.6	0.008	0.503	0.005
Constipation	3.3 ± 2.7	2.6 ± 2.2	2.6 ± 2.3	0.147	0.130	0.468

However, analysis of alimentary diaries showed decreased intake of fibers, calcium, folate, vit D, iron, compared to suggested levels.
Conclusions: Diet with reduced $FODMAP_S$ content improves intestinal and extraintestinal symptoms and quality of life in IBS patients; however, it could be associated with inadequate intake of several nutrients. Thus, a nutritional counseling and follow-up are recommended.

Nonallergic rhinitis with neutrophils: is gastroesophageal reflux disease a possible cause?

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Background: Non-allergic rhinitis (NAR) is defined as a compound of nasal symptoms in the absence of an allergic etiology and it is frequently observed in the clinical practice. Nasal cytology allows to identify the different NAR sub-types on the basis of the particular inflammatory cell infiltrate: non-allergic rhinitis with neutrophils (NARNE), NAR with eosinophils (NARES), NAR with mast cells (NARMA) and NAR with eosinophils and mast cells (NARESMA). The role of GERD in causing extra-esophageal symptoms, such as laryngitis, asthma, chest pain and cough is increasingly recognized with renewed interest but to date, there are no data about the role of the reflux in rhinitis and in particular in the forms with neutrophils (NARNE).
Aim: We aim to evaluate the possible association between gastroesophageal reflux disease and non-allergic rhinitis with neutrophils (NARNE).
Materials and Methods: Between September 2013 and October 2014 thirty-five patients referred to our ENT unit for nasal symptoms such as rhinorrhea, sneezing, and postnasal drip were enrolled. Visual analogue scale (VAS) for nasal obstruction and other NAR symptoms, rhinomanometry, skin prick test and nasal cytology were performed. Exclusion criteria were ambient irritant exposure and/or a positive skin prick test. Of the 35 subjects with NAR, 20 (13F/7M, median age 48 years) showed the presence of neutrophils (neutrophils >50% with absent spores and bacteria) at nasal cytology (NARNE) and were selected to perform a 24 h pH-Impedance. Patients with a 24 h pH-Impedance positive for GERD were treated with a high dose of oral PPI (40 mg × 2/day) for 8 weeks. A second ph-Impedance was performed during therapy, whereas ENT examination and nasal cytology were performed at the end of treatment.
Results: Of the 20 patients with NARNE, 14 (70%) resulted to have pathological basal pH-Impedance values and 6 (30%) resulted to have normal basal values. PH-impedance performed during PPI treatment showed the normalization of the number of refluxes (<48) and pH values (<4.2) in nine (64.3%) out of the 14 patients with positive pH-Impedance at enrollment. Ph-Impedance during treatment continued to be pathological in three (21.4%) patients with a pathological number of refluxes (two with acid pH, one with normal pH values). Two (14.3%) subjects experienced improvement in symptoms and showed the normalization of nasal cytology but refused to repeat the pH-Impedance during therapy. Seven (77.8%) of nine patients with normal ph-Impedance values under treatment showed the simultaneous normalization of nasal cytology, whereas two (22.2%)

subjects did not show any significant improvement at nasal cytology.
Conclusion: This study showed a possible causal association between gastroesophageal reflux disease and non-allergic rhinitis with neutrophils. Treatment with a high dose of oral PPI for 8 weeks seemed to be effective in improving symptoms and in reducing nasal inflammation in a significant number of patients with NARNE. Larger studies are needed to confirm our data.

Impact of esophageal motility in patients with gastroesophageal reflux disease (GERD) non-responders on standard PPI therapy

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Background: Esophageal motility disorder and in particular hypotensive lower esophageal sphincter (LES), impairment of the esophagogastric junction, including both LES and crural diaphragm and ineffective esophageal motility have been strongly implicated in GERD development. Despite treatment with proton pump inhibitors (PPI), some patients with gastroesophageal reflux disease (GERD) continue to have reflux symptoms. Approximately 10 to 40 percent of patients with GERD fail to respond symptomatically, either partially or completely, to a standard dose of PPI. Failure of the PPI treatment to resolve GERD-related symptoms has become the most common presentation of GERD among clinical gastroenterologists.
Aim: To evaluate the impact of esophageal motility in GERD patients who underwent pH-Impedance on standard PPI therapy.
Methods: From November 2013 to September 2014, we retrospectively identified 66 non-responders GERD patients that underwent a pH-Impedance on standard PPI therapy before breakfast and statistically correlated their pH-impedance and manometric parameters to evaluate if the esophageal motility has an impact on pH-Impedance/treatment failure in these patients.
Results: 66 patients (35 F/ 31 M, median age: 50.0 years) underwent pH-Impedance on PPI. 39 of them (59.1%) had a normal pH-Impedance and 27 (40.9%) had a pathological one (11 acid GERD [40.7%], 16 non-acid GERD [59.3%]). Of the 39 patients with normal pH-Impedance, 18 (46.2%) resulted to have a normal manometric tracing and 21 (53.8%) a pathologic one. Among the 27 patients with a pathologic pH-Impedance, 14 (51.8%) had a normal manometry and 13 (48.2%) a pathologic one. The group of the positive pH-impedance patients resulted to have statistically significantly reduced basal pressure of the Lower Esophageal Sphincter (LES) ($p = 0.0082$) and reduced pressure amplitude of the distal esophagus ($p = 0.0165$). The Total Number of Refluxes of the patients in the study resulted to be inversely correlated with the basal pressure of the LES ($p = 0.0004$) and the total number of the nocturnal refluxes resulted to be significantly correlated with the reduced pressure amplitude of the distal esophagus ($p = 0.0487$).
Conclusions: In over 50% of the patients the persisting symptoms, during standard dose of PPI, are not dependent on reflux. The alterations of LES pressure and peristaltic activity negatively influence the success of PPI therapy and, given the significant correlation between manometric alterations and nocturnal reflux, these patients may benefit from an evening dose of PPI. A good portion of patients develop a non-acid reflux disease and may be the best candidates for surgical therapy.

Effects of the pelvic radiotherapy on anal function

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Background: Radiotherapy (RT) is increasingly used for the treatment or the downsizing and downstaging of pelvic tumors but its effects on anorectal function are poorly known.
The aim of the study was to prospectively and comparatively assess the medium-term effects of RT on anorectal function in patients with rectal or prostatic cancer.
Methods: Nine males (mean ± SD; age 67 ± 9 years) undergoing RT for prostate cancer (group A) and 37 consecutive patients with rectal cancer who were candidate to Transanal Endoscopic Microsurgery (TEM) alone or combined with neoadjuvant radio-chemotherapy (n-RCT) were enrolled in the study. In the latter group 10 patients (2 F, 68.8 ± 5 years) underwent n-RCT to downsize the tumor (group B); the remaining 27 patients (F14; 72 ± 5 years) without n-RCT were used as controls (group C).
At baseline, 4 and 12 months after n-RCT/TEM all patients were evaluated with a standardized questionnaire and the Wexner score for fecal incontinence, and underwent recto-anal manometry. Anorectal manometry employed a water-perfused system: pressure at rest and during squeezing, rectal sensitivity and compliance, were evaluated. Mann–Whitney and chi-squared tests were used for statistical analysis.
Results: In all the 3 study groups, the resting pressure at 4 months decreased significantly in comparison with basal conditions (94 ± 11 *vs* 72 ± 15 mmHg, group A; 65 ± 23 *vs* 50 ± 18 mmHg, group B; and 68 ± 23 to 54 ± 26 mmHg group C; $p = 0.04$). Resting anal pressure did not vary at 12 month evaluation in patients with RT *vs* 4 months evaluation (72.6 ± 12.4 mmHg, group A; and 44 ± 11 mmHg, group B), and it returned to basal values in patients without RT (60 ± 30 mmHg, group C).
In the two groups of RT patients (group A *vs* group B), the decrease of resting pressure at 12 months did not differ statistically (−21 ± 12 *vs* −21.4 ± 1.4 mmHg; n.s.), but it was significantly less than in the group without RT (−8 ± 3 mmHg; $p = 0.001$ *vs* both RT groups). Anal squeezing pressure correlated with Wexner score in irradiated patient (r: −0.5). Other manometric variables did not differ statistically between the 3 study groups.
Gas incontinence, soiling and urgency were reported by 25%, 45% and 50% and by 12%, 12% and 38% of the patients in group A, B and C, respectively at 4 and 12 months after treatment (n.s.).
Conclusions: In the management of pelvic tumors, RT reduces anal pressure probably due to the effects on the internal anal sphincter, but such alteration does not cause major anal incontinence.

Peroral endoscopic myotomy (POEM) *vs* Heller Dor (HD) operation for esophageal achalasia: a prospective non randomized comparison

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Aim: POEM is a technique recently introduced for the treatment of achalasia that benefits from the efficacy of myotomy and the advantages of a NOTES technique. This study aims to compare the clinical and physiopathological response of patients treated with conventional POEM *vs* laparoscopic HD procedure.
Methods: 13 patients with diagnosis of primary type 2 achalasia underwent a POEM procedure over a 24 month period (6-2012/7-2014). Pre- and postoperative assessment included: timed barium swallow, endoscopy, high-resolution manometry and Eckardt score evaluation. A 24-h esophageal pH monitoring was performed routinely postoperatively 3 months after the procedure. Patients were treated with PPI for 30 months after the procedures. The data of this group of patients were compared with the data of 13 patients (12 type 2 achalasia, 1 type 1 achalasia), operated on in the same period, who underwent a standard laparoscopic HD procedure. Operation time and preoperative esophageal diameter were also taken into account. The data were compared using Fisher exact test and Mann–Whitney test where appropriate.
Results: There was no statistically significant difference between the two groups for what concerns gender and age. The two groups were comparable for preoperative manometry values, Eckardt score and also for preoperative mean esophageal diameter. The median follow-up time was three months. Eckardt score showed a significant reduction with a median of 0 for both POEM and HD group (Mann–Whitney U-test, $p < 0.0001$). Mean LES resting pressure was 9.2 mmHg (4–14.9 mmHg) in POEM and 8 mmHg (4–11.5 mmHg) in HD group. Median of postoperative DeMeester score was comparable for the two groups, nevertheless endoscopy showed esophagitis in 5 patients (2 LA grade A and 3 LA grade B) in the POEM group and none in the HD group (Fisher exact test, p: 0.02).
Conclusions: POEM is an effective alternative treatment for esophageal achalasia that significantly reduces Eckardt score and LES pressure. The LES resting pressure, according with literature, has higher values in patients who undergo POEM procedure with no statistical relevance. Esophageal acid exposure after POEM and after HD are comparable in the short term follow-up; patients submitted to POEM have a higher incidence of endoscopic esophagitis in the short time ($p < 0.05$).

Diagnostic yield of long-term wireless pH monitoring of the distal esophagus: a ten years single-centre experience

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Long-term (96 h) wireless pH monitoring of the esophagus has been in use for about a decade and is an easy,

widely used and safe way to perform long-term recording. Moreover, it is well-tolerated by patients and has a high sensitivity. Despite the large use, it is still unclear whether or not achieving prolonged recording instead of the more common 48 h monitoring can improve the sensitivity of this test. Our study aimed at reviewing our experience in this field, especially in terms of indications, reliability and diagnostic yield.
One hundred and eighty-nine patients with suspected GERD underwent this particular test from February 2003 to September 2014. The capsule was positioned under endoscopic control, 5 cm above the upper border of the LES. Patients were asked to come back after 48 h in order to restart the recording for other 48 h.
108 patients (57.2%) underwent this study because of intolerance to the traditional pH-catheter, while 78 patients (41.3%) had a previous negative pH study despite symptoms.
All but one patients completed the test (detachment after 6 h), 80 patients (42.3%) had finished their test after 48 h (19 for the early detachment of the capsule) and 108 (57.2%) of the tests lasted ≥72 h.
71 patients had a positive test in the first 24 h (37.6%) and, on the whole, 99 patients (52.4%) in at least one of the 4 days of the study. If we consider only the 96 patients who completed the 96-h test, 46.9% of them were to be considered positive had the test ended after 48 h, but 59.4% if the whole 96-h test was completed, with an increase of more 10% in diagnostic sensitivity ($p = 0.046$).
In conclusion, long-term wireless pH monitoring is reliable, and allows an increased diagnostic yield over traditional pH study. The longer the test, the higher its diagnostic sensitivity.

Single-centre normal values for solid-state esophageal HRM in Italy: a comparison with North-American and North-European values

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Aims: Esophageal High-Resolution Manometry (HRM) has become the reference technology for the assessment of esophageal motor disorders, and prompted the development of the new Chicago Classification, now widely used. However, this is based on normal parameters derived from the original set of 75 volunteers studied at the Northwestern Chicago University. The aim of our study was to provide a new set of normal parameters calculated on a group of Italian healthy volunteers and to compare them to the published North-American (Chicago, IL & Rochester, NY) and North-European (Amsterdam) data sets.
Methods: Thirty-five healthy volunteers underwent Esophageal HRM with a solid-state catheter, with 36 transducers 1-cm apart. Ten wet swallows in the supine position were analyzed using the ManoView® software. Data were expressed as median and 5th–95th percentiles, and the statistical analysis was performed using the Student *t* test with Bonferroni's correction.
Results: The normal range of the different parameters were: EGJ length 3.9 cm (2.6–6.2); EGJ resting pressure: 28.6 mmHg (17–52.6); EGJ 4-s Integrated Relaxing Pressure (4-s IRP): 10.4 mmHg (3.5–17); Intra Bolus Pressure (IBP): 11 mmHg (6.8–18.9); Distal Contraction Integral (DCI): 1641 mmHg*s*cm (514–2965); Contraction Front Velocity (CFV): 3.6 cm/s (2.3–5.7); Distal Latency 6.7 s (4.9–8.5). Most of these figures were similar to previously described parameters. However, the parameters reflecting the contractility strength of the gullet, namely DCI, were lower than the corresponding American values ($p < 0.05$), albeit similar to the European ones (p = n.s.).
Conclusion: Our study provided an additional data set for 'normal' parameters for solid-state esophageal HRM obtained from an Italian population, and demonstrated that differences among volunteers of different countries do exist, thus suggesting caution in the global use of one particular data set of normality.

A critical appraisal of the Chicago classification for the diagnosis of esophageal motor disorders: a prospective study on 35 healthy volunteers and 400 patients

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Aims: High-Resolution Manometry (HRM) has allowed the development of a new classification for esophageal motor disorders (EMDs), named the Chicago Classification, still under continuous revision in order to adapt it to the more recently published data. The aim of our study was to compare the diagnoses of EMDs based on the third iteration of the Chicago Classification with those obtained applying the conventional manometry criteria.
Methods: Thirty-five healthy volunteers and 400 consecutive, untreated patients underwent esophageal HRM with a 36-channel solid-state catheter. Diagnoses were defined by applying the manometric criteria of the traditional classification and, subsequently, by using the last version of the Chicago Classification (CC 3.0). Tracings were analyzed by two expert readers (MC, RS). Symptoms and radiologic or endoscopic data were also used for clarifying the diagnosis in case of major motility disorders (i.e., achalasia).
Results: In 276 cases (69%) the diagnosis obtained with both classification corresponded and the overall concordance index was good (Cohen $K = 0.62$). However, some clusters of mis-diagnoses were found: 44/93 (49.4%) achalasia patients were classified as esophago-gastric-junction (EGJ) outflow ostruction (for the inability to recognize 100% aperistalsis, $n = 35$) or as other peristaltic disorders (for the presence of a normal IRP but absent peristalsis, $n = 11$). All these patients had a good outcome after myotomy or pneumatic dilation. In 11 patients, the diagnosis of EGJ obstruction was determined by an increased IRP (>15 mmHg) and could be corrected in 9 by using our normal value for the same parameter (>17 mmHg). The same was true for the diagnosis of Nutcracker Esophagus, missed in 10 patients with a DCI <5000, but correctly diagnosed with our normal limit (<3000).
Conclusions: HRM has made possible a new classification of esophageal motor disorders. However, only further comparative studies and outcome data may clarify its diagnostic role and impact from a clinical point of view.

Esophageal pH-impedance monitoring in patients with chronic autoimmune atrophic gastritis, upper digestive symptoms and anti-secretory drugs use

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Background & Aims: Patients with chronic autoimmune atrophic gastritis (CAAG) often refer digestive symptoms and are treated with anti-secretory drugs. Aims of the present prospective observational study were to investigate: (i) gastro-esophageal reflux (GER), (ii) psychopathological profile and (iii) anti-secretory drugs use in patients with CAAG.
Methods: Fifty-nine consecutive patients with CAAG were asked to participate. The study protocol included: (i) 24-h intra-esophageal and intra-gastric multichannel intra-luminal impedance-pH (MII-pH) monitoring, (ii) a standardized medical interview (i.e., patients' principal symptom type and frequency, proton pump inhibitors [PPIs] or H_2-receptor antagonists' intake and their effect on the principal symptom, presence of other upper gastrointestinal symptoms, previous *H. pylori* eradication, other diseases or medications' use and results of previous upper gastrointestinal endoscopy) and (iii) SCL-90R validated questionnaire for evaluation of psychological profile. Statistical analysis was performed calculating median and 10th–90th percentiles and risk ratios (RR) with 95% confidence interval (95% CI).
Results: Fifty-two out of 59 patients (31 symptomatic and 21 asymptomatic) agreed to participate in the study. Overall, thirty-one agreed to be investigated with MII-pH: median intra-gastric pH was 6.3 (4.9–7.0), no patients had acid reflux, six patients had an increased number of non-acid reflux and four had positive SI/SAP for an association between symptoms and non-acid reflux; the RR of being symptomatic according to our standardized medical interview, when adjusted for psychological comorbidity, was 1.79 (1.17–2.72) if MII-pH was positive for non-acid reflux. The RR of being symptomatic in patients with altered psychological comorbidity at SCL-90R questionnaire was 1.51 (0.94–2.43) when considering patients with a normal SCL-90R scale as a reference. Antisecretory drugs were prescribed in 16/31 (38%) of the symptomatic patients with a clinical benefit in 11/16 (69%). As assessed by RRs, clinical benefit was independent of psychological comorbidity and non-acid reflux.
Conclusions: Overall, in CAAG patients: (i) acid reflux never occurred, whereas increased non-acid reflux was not infrequent, (ii) symptoms were more frequent in patients with altered psychological comorbidity and (iii) antisecretory drugs were inappropriately used in symptomatic patients. We conclude that MII-pH monitoring is useful in the diagnosis of GER in the minority of patients with CAAG and upper digestive symptoms, and that there is no rationale to prescribe antisecretory drugs.

Analysis of solid swallows at high-resolution manometry unmasks impaired peristalsis in NERD patients with delayed reflux clearance

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	DCI (liquid/solid)	DL (liquid/solid)	CFV (liquid/solid)	TBTT (liquid/solid)
Patients	1428 ± 327*/991 ± 251	6.8 ± 0.4/8.6 ± 1.4*s	4.4 ± 0.6*/3.1 ± 0.4	10.3 ± 1.5/12.2 ± 2.4*s
HVs	1685 ± 546*/1044 ± 324	7.8 ± 0.4/9.8 ± 1.8*s	3.4 ± 0.5*/2.9 ± 0.4	11.2 ± 1.6/13.5 ± 2.6*s

*$p < 0.01$.

Background: Esophageal manometry with liquid swallows has poor sensitivity in demonstrating impairment of esophageal motility in GERD patients. High-resolution manometry (HRM) is considered the gold standard in the study of esophageal motor disorders. Few studies evaluating the esophageal motility during solid bolus swallows are available.
Aim: To comparatively assess the HRM findings during liquid and solid swallows and to evaluate their impact on reflux clearance in GERD patients.
Method: 22 NERD patients with typical symptoms, without hiatal hernia, and 15 healthy volunteers (HVs), underwent HRM combined with impedance (HRM-MI), before and during a 10-min solid meal (bread) in a sitting position. Before meal, a total of 10 liquid (5 mL) swallows, at 30-sec intervals, were performed. A catheter with 36 solid-state pressure sensors and nine impedance segments was used. Following HRM-MI, patients underwent 24-h impedance-pH monitoring (MII-pH). The distal contractile integral (DCI), distal latency (DL) and contractile front velocity (CFV) were calculated according to the Chicago criteria, for both liquid and solid swallows. Esophageal bolus (liquid and solid) clearance was assessed by means of the total bolus transit time (TBTT). The occurrence of >2 cm breaks was assessed in the 20 mmHg isobaric contour. Reflux clearing time (RCT) was calculated in the MII-pH tracings.
Results: Of the 22 patients, 2 with normal MII-pH findings and 5 with hyper- or hypocontractile disorders were excluded. Mean DCI, DL, CFV and TBTT values are in the Table. In all individuals, DL and TBTT were significantly higher during solid, while CFV was higher during liquid swallows. Four HVs displayed, during the liquid swallows, less than two breaks >2 cm. In all HVs (100%) and in 9 out of 15 (60%) patients ($p < 0.05$) the mean DCI values were higher during solid swallows respect to liquid swallows (1685 ± 546 *vs* 1044 ± 324, $p < 0.01$ and 1579 ± 334 *vs* 971 ± 244, $p < 0.01$, respectively). In the remaining six patients, mean DCI values for solid and liquid swallows were comparable (1203 ± 433 *vs* 1021 ± 327). The nine patients with higher DCI presented breaks in 15/90 (17%) liquid swallows and in 28/207 (14%) solid swallows; mean RCT at MII-pH was 12.6 ± 2.7sec; 2/9 displayed abnormal AET. On the other hand, the 6 patients with lower DCI presented breaks in 14/60 (23%) liquid swallows and in 62/167 (37%) solid swallows (p: ns and $p < 0.001$); mean RCT at MII-pH was 15.6 ± 2.2sec ($p < 0.05$ respect to Group 1); 4/6 displayed abnormal AET.
Conclusions: HRM analysis of solid swallows reveals motor abnormalities not detected during liquid swallows. Impaired peristalsis, assessed during solid swallows, may play a role in delaying reflux clearance in NERD patients.

Prevalence of gastrointestinal symptoms and upper endoscopic findings in a population of obese patients candidate to bariatric surgery: a prospective study

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The necessity of routine upper gastrointestinal endoscopy before bariatric surgery is controversial, and the American guidelines for the Perioperative Support of the Bariatric Surgery Patient recommend endoscopy only in symptomatic cases. However, impaired visceral sensation occurring in obese patients may be misleading.
Objectives: To evaluate prospectively in obese patients before surgery, the prevalence of gastrointestinal symptoms, endoscopic findings and the relation between symptoms and endoscopic findings.
Methods: 142 consecutive patients candidate to primary bariatric surgery filled out the validated Rome III symptomatic questionnaire and performed endoscopy to diagnose lesions that could affect the planned procedure. Quantitative data were expressed as median (range). Fisher's exact test was performed and a $p < 0.05$ was considered as statistically significant.
Results: 83% of patients were females, with median age of 41 (range: 17–60) years and BMI of 44 kg/m^2 (range: 35.7–58.7). Antisecretory drugs were taken by 8% of the patients, and 5% reported use of non-steroidal anti-inflammatory drugs (NSAIDs) for cardiovascular prevention. Symptoms were referred by 43% of patients: gastro-esophageal reflux disease (GERD) (27.9%), and dyspepsia (24.6%), subdivided in postprandial distress (PDS) (66.7%) and epigastric pain (33.3%) syndromes. 19.7% of GERD patients presented concomitantly PDS. Belching was present in 8.2%, nausea and/or vomiting in 1.6% of patients. At endoscopy, one or more lesions were present in 47.1% of the patients: erosive esophagitis (5.6%), hiatal hernia (23.2%), gastro-duodenal erosions (6.3%) and peptic ulcers (3.5%). At histology, 24% of patients have *H. pylori* infection and its prevalence in gastroduodenal erosions and ulcers was 22.2% and 60% respectively. Surprisingly in patients with peptic lesions *H. pylori*-negative, no chronic use of NSAIDs was reported. Analyzing the coexistence of symptoms and lesions, these resulted equally distributed beyond presence of symptoms, being present in 44.2% and 49.4% of symptomatic and asymptomatic patients respectively (p = ns).
Conclusions: The presence of symptoms cannot be considered as a valuable guide to indicate endoscopy as the majority of endoscopic lesions were asymptomatic and not *H. pylori*-related. A possible pathogenic role of systemic inflammation in the development of *H. pylori*-negative peptic lesions can be hypothesized.

Baseline impedance values remain stable during the 24-h impedance monitoring

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Aim: Recent data indicate that low esophageal baseline impedance (BI) measurements may reflect the status of the esophageal mucosa and thus may be used to study the role of the impaired mucosal integrity and increased acid sensitivity in patients with heartburn. We aimed to assess any changes of BI levels during 24-h impedance-pH monitoring in patients with heartburn.
Methods: Consecutive patients with heartburn and negative endoscopy underwent 24-h impedance-pH testing off-therapy; then, the 24-h impedance-pH tracings of the patients with abnormal acid exposure time (AET) and/or number of refluxes were manually reviewed to measure mean BI levels during the morning (8 am–1 pm), the afternoon (2–7 pm) and night (8 pm–8 am) by using 15-min windows for each hour and avoiding refluxes and swallowing. Meal time has been excluded from the analysis. Moreover, we specifically compared mean BI during the first pre- and postprandial hour at lunch, dinner and breakfast time.
Results: Out of 40 patients enrolled, twenty showed abnormal AET and/or number of reflux episodes. Overall, we found no differences in terms of mean BI levels during the morning (1122.4 ± 196), afternoon (1163.3 ± 295) and night (1078.3 ± 303) ($p = 0.356$), and no differences during the pre- (1126.9 ± 144) and postprandial time (1053.7 ± 275) ($p = 0.758$).
Conclusions: In patients with heartburn and negative endoscopy, BI levels remain stable during the overall monitoring day, and their values are not influenced by meals or sleeping. Thus, BI level measurements can be performed at any time during the day with high reproducibility.

Impact of upper gastrointestinal symptoms perception on BMI in GERD patients

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Objectives: Upper gastrointestinal symptoms are highly prevalent in the general population and their presence may affect bodyweight by modifying dietary habits and food intake. A significant correlation between high BMI values and GERD has been reported. However, it is not clear whether BMI values correlates with the severity of GERD symptoms, nor it is known the impact of coexisting functional dyspepsia. The aim of our study is to evaluate the relationship between UGI symptoms and BMI in a population of GERD patients.
Methods: 128 (77 F; mean age 42 ± 14 ys; BMI: 29 ± 9) consecutive patients referring for typical GERD symp-

toms (heartburn and regurgitation) were enrolled. All patients underwent history taking, UGI-endoscopy and off-therapy 24 h-pH-impedance monitoring. GERD and FD symptoms were scored according to standardized questionnaires. Presence and severity of upper-GI symptoms and their impact on quality of life was evaluated using PAGY-SYM and PAGY-QoL questionnaires, respectively. In addition, a correlation analysis was run looking at the specific items regarding the impact of symptoms on eating.

Results: Overweight and obesity were present in 21.5 % and 28.1% of the patients, respectively. In obese subjects the severity of GERD symptoms was significantly lower than in over- and normo-weight patients (6.8 ± 8.6 *vs* 13.7 ± 8.5 and 13.2 ± 10, respectively; all $p < 0.01$) and this was confirmed by the significant negative correlation between BMI and GERD severity score (r^2: 0.12; 95% CI −0.49 to −0.2, $p < 0.01$) No differences were observed in pH-impedance parameters, except for the number of total proximal refluxes that was higher in the obese than in the normo-weight, but not in overweight patients (42 ± 22 *vs* 31 ± 21 and 40.6 ± 17 respectively, $p < 0.05$). In obese patients the prevalence of FD was also significantly lower than in over- and normo-weight patients (25 *vs* 51 and 66%, $p < 0.05$ and $p < 0.01$, respectively). Accordingly obese subjects reported lower dyspepsia symptoms severity, than normo-, but not overweight patients (7.9 ± 10.9 *vs* 17.5 ± 14.3 and 14 ± 12, $p < 0.01$). An inverse correlation between dyspepsia intensity score and BMI was registered (r^2: 0.13; 95% CI −0.5 to −0.21, $p < 0.01$). Interestingly, intensity scores of both GERD and FD symptoms showed a positive correlation with the score assessing eating behavior changes (GERD: r^2: 0.09, 95% CI 0.16–0.45, $p < 0.01$; FD: r^2: 0.26, 95% CI 0.39–0.62; $p < 0.01$).

Conclusions: In this study we showed that high values of BMI are associated with a lower perception of GERD and dyspepsia symptoms, suggesting a reduced visceral sensitivity in overweight and obese patients. Alternatively, our data indicate that the increased severity of upper GI symptoms may affect bodyweight by modifying dietary habits and reducing calories intake. Although mechanistic studies are needed, we conclude that UGI symptoms may represent a protective factor against obesity.

Esophagogastric junction contractility for clinical assessment in patients with GERD: a real added value?

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Objectives: Different mechanisms have been involved in gastroesophageal reflux disease (GERD) pathogenesis and their specific roles are still under investigation. In particular, the esophagogastric junction (EGJ) contraction at rest is considered a major defense against gastroesophageal reflux. Recently, a new high-resolution manometry (HRM) metric, the EGJ-contractile integral (EGJ-CI), was proposed to quantify the vigor of EGJ, trying to assess a correlation between the contractility strength and acidic reflux exposure. The EGJ-CI resulted to be useful in distinguishing patients with functional heartburn from those with PPI resistant GERD. However, impedance-pH and endoscopy findings in relation to EGJ-CI are still very poor. Hence, our study aimed to correlate the EGJ-CI with impedance-pH findings in patients with GERD, by assessing the predictive value of the EGJ-CI in diagnosing GERD at impedance-pH and the correlation of this metric with different EGJ morphological subtypes and endoscopic findings.

Methods: Consecutive patients with GERD symptoms were enrolled. All patients underwent upper endoscopy, HRM and impedance-pH testing off-therapy. EGJ-CI was calculated using the distal contractile integral tool box during three consecutive respiratory cycles with a threshold of 2 mmHg above the gastric pressure. The value was then divided by the duration of three respiratory cycles. A value below 13 was considered as a defective EGJ-CI. We also assessed EGJ morphology, esophageal acid exposure time (AET), number of reflux episodes (NRE), and symptom association analysis (SAA). Receiver operating characteristic (ROC) curves were used for estimating the optimal cut-off value for a GERD diagnosis. Univariate and multivariate analysis were performed for testing the predictive potential of EGJ-CI in terms of positivity at impedance-pH monitoring.

Results: Among 130 patients we enrolled, 91 had GERD (abnormal AET and/or elevated NRE and/or positive SAA) and 39 had functional heartburn (FH) (negative endoscopy, normal AET, normal NRE, and negative SAA). GERD patients had a lower value of median EGJ-CI (11 [3.1–20.7] *vs* 22 [9.9–41], $p < 0.02$) compared to FH patients. Patients with a defective EGJ-CI had more frequently a positive impedance-pH monitoring, or an abnormal NRE, or a pathologic AET ($p < 0.05$, $p < 0.001$, $p < 0.002$, respectively) than patients with a normal EGJ-CI. Patients with negative endoscopy showed a higher median value of EGJ-CI (16.7 [7.4–33] *vs* 4 [0.2–14.5], $p < 0.001$, *vs* 7.8 [2.1–14.6], $p = 0.06$) than ERD and Barrett's esophagus. An EGJ-CI cut-off value of 5 mmHg cm yielded the optimal performance in identifying impedance-detected GERD (sensitivity 89%-specificity 63%).

Conclusions: The results of our study suggest that patients with a defective EGJ-CI had a significant increase in reflux episodes and esophageal acid exposure, thus making the diagnosis at impedance-pH monitoring, while off-PPI therapy, more reliable. Thus, given the relatively easy feasibility of EGJ-CI assessment during HRM, these findings emphasize the utility of performing EGJ vigor assessment during manometry protocol and describing its value.

Oxidative stress-induced alterations of vasoactive intestinal peptide (VIP)- pathway in human gastric antrum in obese patients

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Aims: Obesity is characterized by systemic oxidative status and low grade inflammation. Production of Reactive oxygen species is increased in adipose tissue of obese humans, due to an upregulation and expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and a downregulation of antioxidative enzymes. Genome-wide association analysis has identified a significant association between the vasoactive intestinal peptide (VIP) pathway and obesity. VIP is an enteric neuropeptide involved in muscle relaxation and our previous studies have highlighted that in human antrum, VIP causes greater relaxation mainly by interacting with VPAC2 coupled to the cAMP signaling pathways. The aim of this study was to evaluate in obese patients VIP and related signaling pathways effects on smooth muscle of gastric antrum and to evaluate the influence of redox state.

Methods: Smooth muscle cells (SMC) and strips were isolated from human gastric antrum obtained from 14 normoglycemic-normo-cholesterolemic morbid obese patients (40.9 < BMI < 52.0 kg/m^2; 37 < age < 45 years) submitted to sleeve gastrectomy and 9 patients submitted to gastrectomy for gastric cancer (control: 19.0 < BMI < 25.0 kg/m^2; 56 < age < 75 years). VIP (1 μM) relaxant effects were tested on maximal cholecystokinin (CCK 1 nM)-induced contraction on SMC and strips while the effect of adenylate cyclase activator forskolin (FSK, 10 mM) and the 2nd messengers cAMP (0.1 mM) only on SMC. qPCR analysis was performed for transcripts for VPAC2, and inflammatory cytokine (COX-2), the data were normalized to β-actin mRNA levels. Oxidant capacity in obese SMC was evaluated by antioxidant assay kit and by the use of NADPH inhibitor Apocynin (APO: 1 μg/mL) or the antioxidant drug *N*-Acetyl-Cysteine (NAC:5 mM). Data are expressed as mean ± SE, $p < 0.05$ considered significant.

Results: This study shows a hyporesponsiveness of human gastric antrum smooth muscle to VIP in obese patients. In the obese, VIP-induced relaxation was significantly reduced both on muscle strips (13.8 ± 5.2%) and SMC (14.5 ± 7.3%) in comparison to control (strips: 78.1 ± 7.4%; SMC: 79.96 ± 5.78%). The SMC relaxation induced by second messenger cAMP and FSK, was significantly reduced in comparison to control (cAMP: 44.9 ± 7.6 *vs* 73.4 ± 5.8%; FSK: 54.95 ± 2.3 *vs* 71.80 ± 11.8%). This hyporesponsiveness to VIP was associated in SMC with a significant decrease in VPAC2 messenger (obese: 3.63 ± 0.06 *vs* control: 6.27 ± 0.79), and an increase in COX2 messenger (obese: 4.93 ± 0.63 *vs* control: 1.10 ± 0.08). At the same time a substantial oxidant capacity was observed (0.06 ± 0.003 equivalent of trolox). In the presence of APO all the alterations observed were partially restored. APO pretreatment of obese SMC induced: a complete restoration of the VIP-induced relaxation 79.60 ± 11.84, a significant increase in VPAC2 messenger expression (4.02 ± 0.03) and a significant decrease in oxidant capacity (0.0035 ± 0.002 equivalent of trolox). In addition with NAC pretreatment VIP-induced relaxation was recovered by 77.9 ± 11.4% and VPAC2 messenger expression 3.8 ± 0.05.

Conclusions: In obese patients, intrinsic SMC oxidative stress altered the VIP pathway mediating relaxation both receptor level and intracellular signaling pathways.

Increased frequency of swallows during 24 h in NERD non-responders to proton pump inhibitors

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Background: It has been demonstrated that NERD patients not responding to PPIs are characterized,

respect to responders, by an increased overall number of refluxes and by enhanced sensitivity to mixed and proximal reflux episodes. It has been also shown that non-responders swallow more air at mealtime than responder patients.
Aim: To explore the relationship between swallowing and reflux pattern in 24 h in NERD patients responding or not to PPIs.
Methods: MII-pH was performed, after a washout from PPIs, in 41 NERD non-responders and in 70 responders to double dose of PPIs, presenting with typical symptoms, following esophageal manometry. All patients filled out a questionnaire with symptom score. Acid exposure time (AET) and Symptom Association Probability (SAP) indexes were calculated. For each patient, swallows were evaluated during the entire length of MII-pH study, excluding the meal period. Air swallowing was also assessed. Due to the high frequency of artifacts, the meal period was excluded from the analysis. Patients were instructed to have 3 meals and 4 beverages at fixed times.
Results: 11 non-responders (4 with ineffective esophageal motility, 7 with normal AET and SAP) and 20 responders (9 with ineffective esophageal motility, 11 with normal AET and SAP) were excluded thus 30 non-responders and 50 responders were studied. Nine non-responders and 29 responders showed a pathological AET. Non-responder patients were characterized, compared to responders, by a higher overall number of reflux episodes (median, 25th–75th percentile; 67, 43–94 *vs* 42, 31–65, $p < 0.01$). The proportion of weakly (41% *vs* 39%), mixed (46% *vs* 44%) and proximal (53% *vs* 47%) reflux episodes did not differ between non-responders and responders. During MII-pH, non-responders swallowed more frequently than responders (mean ± sd, 445 ± 112 *vs* 381 ± 89, $p < 0.05$). The swallow rate per hour was 19 ± 4.9/h in non-responders and 16.6 ± 3.9/h in responders. In both non-responders and responders the swallowing frequency significantly decreased during sleep (13.3 ± 1.2/h and 11.4 ± 0.8/h, $p < 0.01$). Swallows were followed by reflux episodes after 56.5 ± 18.4sec. in non-responders and 75 ± 22.8 in responders ($p < 0.01$). The frequency of air swallows was comparable between the two groups (56% *vs* 49%).
Conclusions: Non-responder NERD patients are characterized by an increased frequency of swallows during 24 h. This finding may explain the increased number of reflux episodes observed in non-responder patients, and further support the role of mucosal sensitization in this subgroup of patients.

Relevance of mixed reflux and weak peristalsis with delayed reflux clearance in chest pain perception in NERD patients

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Introduction: Mechanisms underlying non-cardiac chest pain (NCCP) are still to be fully elucidated. Gastroesophageal reflux disease (GERD) appears to be the most common cause, while esophageal dysmotility seems to play a limited role in symptom generation. High-resolution manometry (HRM) allows to accurately evaluate esophageal motility.
Aim/Methods: To evaluate whether different mechanisms may account for NCCP and heartburn in NERD patients, of consecutive patients, those presenting both symptoms but NCCP as major symptom underwent, following a washout from PPIs, ambulatory 24-h pH-impedance monitoring following an HRM study (36 solid-state sensors catheter). An *ad hoc* questionnaire focused on the type, frequency and impact of symptoms was obtained from each individual. Tracings of 41 NERD patients reporting both symptoms during the study (group 1) were analyzed and data were compared to those obtained in 50 NERD patients presenting with heartburn only (group 2). In all patients, NERD diagnosis was confirmed by pH-impedance monitoring. Reflux clearance time (RCT), i.e., time frame between reflux entry and exit, was calculated at 5, 9, and 15 cm above the LES. Acid exposure time (AET) was calculated according to the described criteria. Presence of motor abnormalities was assessed according to the Chicago criteria.
Results: 26/41 (63%) NERD patients belonging to group 1 and 12/50 (24%) to group 2 presented weak peristalsis with small or large breaks at HRM ($p < 0.05$). Two patients of group 1 and 4 of group 2 showed findings of hypertensive peristalsis. Reflux frequency (mean ± SD, 62 ± 24, 56 ± 31) and symptom occurrence (mean ± SD, 6.1 ± 3.1, 5.7 ± 2.8) were comparable in the two groups. AET was positive in 18/41 group 1 and in 24/50 group 2 patients (*p*: ns). Characteristics of reflux episodes are in the Table. In group 1 (NCCP), chest pain episodes were mostly associated with mixed refluxes (Odds Ratio, 95% CI, 1.72, 1.1–2.6) while heartburn episodes were mostly associated with proximal refluxes (1.76, 1.2–2.9). In group 1, RCT in NCCP-associated refluxes at 5, 9, and 15 cm was higher than that observed in heartburn-associated refluxes (mean ± 95% CI; 26.5 ± 5.5, 22.3 ± 4.2 and 14.1 ± 2.3 s *vs* 18.3 ± 3.5, 13.3 ± 2.2 and 11.1 ± 1.8 s, $p < 0.01$) and that in asymptomatic refluxes (13.3 ± 1.5, 12.3 ± 1.2 and 9.8 ± 0.9 s $p < 0.01$). RCT of NCCP-associated refluxes, in group 1, was higher than that observed for heartburn-associated refluxes in the group 2 patients (17.1 ± 2.5, 12.2 ± 1.2 and 12.1 ± 1.4 s, $p < 0.01$).
Conclusions: Weak peristalsis is more frequently observed in NERD patients with predominant NCCP. The presence of gas in the refluxate, likely associated with high-volume reflux episodes, seems to be associated with NCCP perception. The impaired motility observed in patients with NCCP may play a relevant role in delaying reflux clearing and, hence, increasing the time of contact between refluxate and esophageal mucosa.

	NCCP patients			Patients with heartburn only
	NCCP-associated refluxes (%)	Heartburn-associated refluxes (%)	Asymptomatic refluxes (%)	Heartburn-associated refluxes (%)
Acid refluxes	66	59	31	62
Mixed refluxes	79*	52	53	47
Proximal refluxes	38	67*	36	59

*$p < 0.01$.

Findings of impedance pH monitoring in patients with typical and atypical gastroesophageal reflux symptoms: experience from 'real-world' utilization

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Objectives: The aim of the study was to compare clinical and esophageal pH-impedance data of patients referring to our Gastro-Lab in 2013 for the assessment of symptoms possibly due to GERD, in the absence of endoscopic esophageal lesions, either typical or atypical (i.e., chest pain, cough, pharyngeal globus).
Methods: One hundred and sixty-one adult patients (108 females, 53 males, mean age 44 years) were evaluated for both typical and atypical NERD symptoms refractory to PPI therapy: 90 patients had atypical symptoms (80 of them off-therapy, 10 on therapy) and 71 typical symptoms (52 being off-therapy, 19 on therapy).
Results: In the typical symptoms group, heartburn was the only symptom in 52/71 (73%); heartburn and regurgitation were predominant symptoms in 7/71 (10%); regurgitation only in 3/71 (4%); cough and heartburn in 4/71 (6%); chest pain and heartburn in 2/71 (3%), globus and heartburn in 3/71 (4%). In the atypical symptoms group, globus was complained of in 33/90 (37%); cough in 20/90 (22%); chest pain in 20/90 (22%); other symptoms, such as cardiac arrhythmia, dysphagia, dysphonia, epigastric pain, pharyngodynia, laryngitis, hypersalivation in 17/90 (19%). Table 1 shows esophageal pH-impedance analysis data in the two subgroups (only for off-therapy patients).
Conclusions: The percentage of patients with a pathological pH-impedance is significantly greater in the typical symptoms group. Overall, in less than half of the patients, a diagnosis of GERD-related symptoms was achieved and this figure is substantially lower in patients with potentially GERD-related atypical symptoms. We confirmed that achieving a diagnosis in patients with so-called atypical GERD symptoms, and in particular with pharyngeal globus, is challenging.

Table 1

	Typical ($N = 52$)	Atypical ($N = 80$)	χ^2
Esophageal acid exposure >4.2%	54% (28/52)	24% (19/80)	$p = 0.0008$
Proximal extension (>64%)	2% (1/52)	3% (2/80)	ns
Symptom correlation (SAP >95%)	35% (18/52)	24% (19/80)	ns
Bolus Clearance Time (BCT >20 s)	2% (1/52)	4% (3/80)	ns

Table 1

Achalasia	Type I	2.8% (*N* = 11)
	Type II	6.9% (*N* = 27)
	Type III	1.2% (*N* = 5)
EGJ outflow obstruction		1.2% (*N* = 5)
Motility disorders	Distal esophageal spasm	2.2% (*N* = 9)
	Hypercontractile esophagus (Jackhammer esophagus)	2.1% (*N* = 8)
	Absent peristalsis	3.2% (*N* = 13)
Peristaltic abnormalities	Weak peristalsis with large peristaltic defects	7.0% (*N* = 28)
	Weak peristalsis with small peristaltic defects	1.2% (*N* = 5)
	Frequent failed peristalsis	11.7% (*N* = 47)
	Rapid contractions with normal latency	1.2% (*N* = 5)
	Hypertensive peristalsis (Nutcracker esophagus)	3.0% (*N* = 12)
	Scleroderma esophagus with absent peristalsis	1.2% (*N* = 5)

High-resolution esophageal manometry and the Chicago classification: how they impact the clinical practice

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Objectives: High-resolution (HR) esophageal pressure topography is an evolutionary technology incorporating the combination of high-resolution manometry (HRM) and pressure topography plotting, which has been introduced by the late R. Clouse in 2000 for the clinical evaluation of esophageal motility. We report here the activity of our esophageal HR manometry laboratory at 'Bolognini' Hospital in Seriate, Bergamo, during the period from June 2012 to now.
Material and Methods: In June 2012, we shifted from conventional ambulatory esophageal manometry to high-resolution (HR) manometry. 403 manometries have been performed as for the investigation of many different upper GI symptoms such as dysphagia, odynophagia, non-cardiac chest pain, globus, or for the preoperative assessment of GERD patients. The median age was 48 years, the F/M ratio 1.1/1. The Chicago classification (Pandolfino JE *et al.* Am J Gastroenterol 2008; 103:27–37) was used in order to characterize and classify the manometric data into the corresponding esophageal motility disorders.
Results: A slight majority of patients proved to have a normal esophageal motility (*N* = 222 [55.2%]). Table 1 shows the remaining diagnoses.
Conclusion: This retrospective analysis shows, in large series of patients referred to a tertiary centre, that HR manometry helps in fine characterizing the esophageal motility disorders. The conclusion that can be drawn from this study is that secondary motility disorders are very infrequently investigated by HR manometry and that peristaltic abnormalities (in particular frequently failed peristalsis and weak peristalsis with large defects) and achalasia are the most frequent diagnoses.

Automatic diagnosis of esophageal motor disorders from HRM data

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Aims: In order to support the traditional diagnostic process of esophageal motor disorders and to remove the inter- and intra-observer variability, an automatic diagnosis procedure was here defined to autonomously recognize esophageal motor disorders from HRM data.
Methods: The automatic diagnosis procedure was designed accounting for a specific physiological model able to interpret data from esophageal HRM:

$$p(x,t)=s(x,t)+\delta(x,t)$$

$$\text{with } s(x,t)=p_0(x)+[p_{max}(x)-p_0(x)]\,\text{sech}\left\{\tfrac{\beta(x)}{L}[x-\eta(x)t]\right\}$$

$$\delta(x,t)=\tfrac{5}{4}\Delta(x)\left\{\tanh\left[\tfrac{2}{\phi(x)}\left(t-\tfrac{x}{\eta(x)}\right)\right]-\tfrac{1}{5}\tanh\left[\tfrac{2}{5\phi(x)}\left(t-\tfrac{x}{\eta(x)}\right)\right]\right\}$$

where t is time, x is the normalized position along the esophageal axis ranging between 0, as the UES, and 1, as the LES, L is the esophageal length, as the distance between UES and LES, $p_0(x)$, $p_{max}(x)$, $\eta(x)$, $\beta(x)$, $\Delta(x)$ and $\phi(x)$ are the model parameters.
A training set of 226 pathological subjects and 35 healthy volunteers was firstly collected, and the corresponding model parameters were identified by minimizing a specific cost function. Such function represents the discrepancy between experimental data and model results, and can be minimized by means of specific iterative procedures. According to the developed algorithm, a subject can be classified by computing a specific similarity index between its model parameters and the parameters distributions of the different groups. The subject was finally assigned to the group showing the highest similarity index.
Results: Different healthy or pathological conditions were investigated, and the data set was subdivided into groups, as non-pathological subjects (106 patients + 35 volunteers); achalasia pattern 1 (35 subjects), achalasia pattern 2 (49 subjects), hypertensive LES (9 subjects), nutcracker esophagus (15 subjects), and diffuse esophageal spasm (12 subjects). With regard to each group of subjects, the identified model parameters were statistically processed in order to assess their statistical distributions. The global success rate of the algorithm was 85.71%, being maximum in achalasia (89.4%) and minimal in the hypertensive LES group (55.5%).
Conclusions: The results suggest the suitability of the model to interpret data from esophageal HRM, and address the reliability of the procedures developed to provide a valid support to the clinicians for the diagnostic activity. The procedure should be refined, extended and tested accounting for a larger group of patients data, hopefully multicentric, which is required for a further validation of the process.

Clinical utility of genetic test in negative lactose breath testing

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Introduction: As known, false-negative lactose breath testing (BT) can occur in about 20% of cases. The C/T-13910 polymorphism on chromosome 2q21 has been found to be completely associated with lactase activity and proposed as a genetic test (GT) in adult-type hypolactasia. According to recent evidences GT could permit the exclusion of false-negative results after a traditional H2-BT.
The aim of our study was to demonstrate the diagnostic advantage of GT in patients with negative lactose BT.
Methods: In a period of 6 months, we have prospectively evaluated 12 patients (8 female; mean age 31.4 years) with negative BT who gave their consent to perform genetic test and a control group of 15 subjects (11 female, mean age 36.7 years) with a negative BT as a unique test. In the same period a total of 476 patients have performed the lactose BT: 82% was positive, 18% negative. To perform BT, breath samples were taken at fasting and every 30 min for 4 h after the administration of 25 g of lactose. The test was considered negative when H2 values were lower than 20 ppm over the baseline. Genomic DNA was isolated from peripheral blood using a salting-out procedure (Miller *et al.*, 1988) and genotyped for the C/T-13910 polymorphism according to Buning *et al.* (2003). In detail the C/C-13910 genotype was associated with lactase non-persistence (hypolactasia) while the T/C-TT-13910 genotype with lactase persistence. Finally the presence of abdominal pain, bloating, flatulence and diarrhea was recorded in all patients during the test and 8 h after.
Results: Among patients with negative BT, GT showed a C/C genotype suggestive for hypolactasia in 10 (83%), only two had a T/C genotype suggestive for normolactasia, confirming BT results. If these results were compared with the control group, where GT was not available, a highly significant diagnostic gain was achieved with GT ($p < 0.0001$). Finally, the analysis of symptoms showed a significant major frequence of symptoms in the genetic group (also present in normolactasic subjects) than controls (83% *vs* 33%: $p = 0.005$).
Conclusions: In our country, where up to 90% of general population is hypolactasic, negative BTs are diagnosed in a minority of patients (15–18%). With respect to GT, most of negative BT patients in our series were surprisingly hypolactasic disclosing a false-negative BT in a high percentage. The presence of symptoms in negative BT could be considered a predicative factor for hypolactasia. Besides symptomatic patients can find a stronger motivation to perform GT after a negative BT. Our study suggests that GT, where available, can be recommended in case of negative BT. These data should be however confirmed in a higher number of patients.

Effect on anal function after transanal endoscopic microsurgery (TEM) and radiotherapy for distal rectal cancer

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Ano-rectal function impairment has been reported after total mesorectal excision and Radiotherapy for pelvic tumors[1], but no study evaluated the effects of neoadjuvant radiochemotherapy (n-RCT) on anorectal function in patients with distal rectal cancer who undergo minimally invasive surgical treatment such as TEM. The effects of either treatment, alone or combined, have not been adequately investigated.

Aim: The aim of the study was to prospectively and comparatively assess the medium-term effects of anorectal function after TEM and n-RCT for distal rectal cancer.

Methods: Thirty-seven consecutive in-patients with rectal cancer and nine control patients with prostate cancer were enrolled. At baseline, 4 and 12 months after RT all patients were evaluated with a standardized questionnaire and the Wexner score for fecal incontinence, and underwent recto-anal manometry. Extraperitoneal rectal tumors staged ≤T2 N0 and/or with size ≤4 cm at diagnosis time or after irradiation were submitted to TEM. Anorectal manometry was performed using a water-perfused system: pressure at rest and during squeezing, rectal sensitivity and compliance, were evaluated. Mann–Whitney and chi-squared tests were used for statistical analysis.

Results: Twenty-seven patients (14 F, 72 ± 5 years, mean ± SD) underwent TEM without n-RCT (group A); 10 patients (2 F, 68.8 ± 5 years) underwent TEM after n-RCT (group B); 9 M, (67 ± 9 years) underwent RT for prostate cancer (group C).

In group A mean anal resting pressure decreased from 68 ± 23 to 54 ± 26 mmHg at month 4 ($p = 0.04$) after surgery and returned to normal values 12 months postoperatively (60 ± 30 mmHg). In group B and C, respectively, mean anal resting pressure decreased from 65 ± 23 to 50 ± 18 mmHg and from 94 ± 11 to 72 ± 15 mmHg at month 4, and remained stable 12 month postoperatively (44 ± 11 mmHg, $p = 0.04$ and 72.6 ± 12.4 mmHg, $p = 0.001$ *vs* preoperative values and ns *vs* 4 month postoperatively).

The anal resting pressure differences between basal and 12 months after irradiation of group B and C was similar and was significantly lower than group A ($p = 0.001$). Gas incontinence, soiling and urgency were reported by 50%, 45% and 25% and by 38%, 12% and 12% of the patient group A, B and C, respectively at 4 and 12 months after treatment.

Conclusions: The results of this study indicate that TEM *per se* does not significantly affect anal function. N-RCT to obtain downstaging and downsizing of distal rectal cancers, in order to perform TEM, affects resting anal pressure but it does not cause major anal incontinence.

Reference:

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Protective effect of inulin on LPS-induced oxidative stress of human colonic mucosa

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Backgrounds and Aims: Fructans, such as inulin, are dietary fibers which stimulate gastrointestinal function acting as prebiotics. We recently demonstrated the protective effect of inulin on LPS-induced damage of colonic smooth muscle in an *ex vivo* experimental model, which seems to be related to presence of oxidative stress. In this study, antioxidant properties of inulin and its protective role against LPS-induced oxidative stress were evaluated on colonic mucosa.

Methods: Human colonic mucosa and submucosa, obtained from disease-free margins of resected segments for cancer, were sealed between two chambers containing Krebs solution, with the luminal side of the mucosa overlayed with 5 mL of Krebs, or 100 μg/mL LPS solution, or 100 μg/mL LPS +100 mg/mL inulin Fructafit IQ (LPS+INU). The biological system was kept oxygenated for 30 min at 37 °C. Protein oxidation was evaluated in the colonic mucosa by measuring carbonyl group content using the dinitrophenylhydrazine and measuring the formed complex by spectrophotometric analysis. Total antioxidant capability of fructans, with different degrees of polymerization (DP – 8–125), was analyzed by the TEAC method and compared with the antioxidant activity of simple sugars forming fructan polymers (glucose, fructose, and sucrose). iTRAQ based analysis was used to separate and compare the total soluble proteomes from human colonic mucosa and submucosa treated. Each sample was labeled by one of four reagents of the iTRAQ 4-plex and then combined into one aliquote. Triplicate labelling were performed, which showed a high level of reproducibility.

Results: All the tested fructans showed greater antioxidant capability than sucrose, glucose and fructose. The antioxidant activity of IQ was not affected by treatments at high temperature, as well as by pH changes and exposure to digestive enzymes. By measuring inulin in the model undernatants, we found that inulin did not cross the colonic mucosa layers. When the colonic mucosa was exposed to LPS+INU, the amount of the colonic mucosa carbonyl groups was reduced of about 60% compared to LPS exposed mucosa. The ROS protecting effects of inulin was also discussed in the light of the results obtained by proteomic analysis.

Conclusion: Inulin protects the human colon mucosa from LPS-induced oxidative stress. Our preliminary data suggest that the beneficial effects of inulin on the health of the host could be related, not only to its bifidogenic action, but also to its antioxidant properties.

Autoimmune comorbidities in idiopathic achalasia

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Objective: The pathogenesis of achalasia has not been clarified yet, but recent genetic studies indicate a significant association with genes involved in immune response. These observations likely support the concept that achalasia is an autoimmune disease. A single center study report a higher prevalence of autoimmune comorbidities in achalasia as compared to the general population (1). Here we evaluated the presence of autoimmune comorbidities in a large cohort of achalasia patients compared to a matched control population.

Methods: We retrospectively evaluated 230 patients (95 males, mean age 55 ± 18 years) with proven clinical and instrumental diagnosis of idiopathic achalasia. Subjects selected from the outpatient clinic and referring of other esophageal disorders rather than achalasia, served as gender and age matched controls. In all patients, the presence of comorbid autoimmune diseases was recorded. The impact of comorbidities on achalasia phenotype and age of disease's onset was also analyzed.

Results: Though the overall prevalence of autoimmune disorders was similar to that of the control population, a slight tendency to a higher prevalence in achalasia (8 *vs* 5%, p = NS) was observed, without any difference for each of the considered autoimmune diseases. Hashimoto's thyroiditis and Graves' disease were the most frequently reported autoimmune comorbidities in achalasia patients and controls (7% *vs* 8% 0.8% *vs* 1% respectively, p = NS). Furthermore, presence of comorbidities did not significantly affect disease's phenotype as the age of disease onset was similar in achalasia patients with and without comorbidities (46 ± 21 *vs* 49 ± 16 years, respectively, p = NS).

Conclusions: This study shows that idiopathic achalasia, though considered an autoimmune disorder, seems not to be related with comorbid autoimmune diseases. Although larger epidemiological studies are warranted to confirm our data, our results indicate that the putative genetic background associated with achalasia is specific for the disorder.

Reference:

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Esophageal motility alterations in neurologic disease

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Neurologic diseases can be affected by dysphagia, with alterations of the several phases of swallowing. We know that in patients affected by amyotrofic lateral sclerosis (ALS) or stroke there are alterations of the oral phase, but poor is known about alterations of esophageal motility.

The aim of our study was to assess the frequency of esophageal motility in ALS and stroke.

Material and Methods: Forty-five patients (27 M; median age 59 ± 12 years) affected by ALS and 35 patients (20 M; median age 67 ± 9 years) affected by stroke underwent videofluoroscopic swallowing study (VFSS) with taperecording for slow motion analysis of the images to assess esophageal motility alterations. VFSS was performed in the anteroposterior and lateral upright position for the assessment of the oro-pharyngeal and esophageal phase. During this study, videorecording of

	Stroke pts (n = 35)	ALS pts (n = 45)	p
Esophageal hypotonia (n = 18)	6	12	ns
Delayed esophageal clearing time (n = 66)	32	34	ns
No peristaltic contractions (n = 35)	23	12	0.006
Aperistalsis (n = 4)	2	2	ns
Non-coordinated LES opening (n = 9)	3	6	ns

swallowing of a variety of boluses with different consistencies (semiliquid, semi-solid of increasing volumes, liquid and solid) was performed for subsequent analysis. In each patient, we studied the presence of the following esophageal motility alterations: esophageal hypotonia, delayed esophageal clearing time, no peristaltic contractions, aperistalsis, no coordinated lower esophageal sphinter (LES) opening.

Results: All patients affected by stroke have at least one esophageal motility alteration. 36 patients affected by ALS presented one or more esophageal alterations. No peristaltic contractions were more frequent in patients affected by stroke than ALS (p = 0.006). The table summarizes the results.

Conclusions: These observations demonstrate not only that esophageal motility alterations are present in ALS and in stroke, but also that no peristaltic contractions are more frequent in stroke. Further studies are necessary to understand the cause of esophageal alterations and the role in etiopathogenesis of dysphagia in neurologic patients.