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**Oesophageal Motility And Bolus Transit Abnormalities
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For Peer Review

Oesophageal Motility And Bolus Transit Abnormalities Increase In Parallel With The Severity Of Gastro-Oesophageal Reflux Disease

Edoardo Savarino MD, PhD^{1,2}, Lorenzo Gemignani MD¹, Daniel Pohl MD², Patrizia Zentilin MD, PhD¹, Pietro Dulbecco MD¹, Lorenzo Assandri MD², Elisa Marabotto MD¹, Daria Bonfanti MD¹, Simona Inferrera MD¹, Valentina Fazio MD¹, Alberto Malesci MD³, Radu Tutuian MD⁴, and Vincenzo Savarino MD¹.

¹Division of Gastroenterology, Department of Internal Medicine, University of Genoa, Genoa, Italy

² Division of Gastroenterology and Hepatology, Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland

³ Division of Gastroenterology, IRCCS Istituto Clinico Humanitas, Milan, Italy

⁴ Bern University Hospital, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland

Running title: Abnormal Bolus Transit in GORD patients and FH.

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Corresponding author:

Edoardo Savarino, MD, PhD

Di.M.I. Cattedra di Gastroenterologia, Università di Genova

Viale Benedetto XV

16132 Genova, Italy

Tel.: 0039-010-3538956

Fax.: 0039-010-3538956

Email: edoardo.savarino@unige.it

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ABSTRACT (Word count 241):**Introduction:**

Limited data are available regarding the frequency of oesophageal motility and bolus transit abnormalities in subgroups of patients with gastro-oesophageal reflux disease (GORD).

Aim:

To assess oesophageal motility and bolus transit in endoscopically-defined GORD subgroups.

Methods:

Patients (N=755) with typical reflux symptoms underwent upper endoscopy, conventional or impedance oesophageal manometry and/or impedance-pH testing. They were divided into: erosive oesophagitis (EO; N=340), Barrett Oesophagus (BO; N=106), non-erosive reflux disease (NERD; endoscopy-, abnormal pH and/or SAP/SI+; N=239) and functional heartburn (FH; endoscopy-, normal pH and SAP/SI-; N=70). Manometric patterns and bolus transit were defined according to previously published criteria.

Results:

Increasing GORD severity was associated with decreased lower oesophageal sphincter resting pressure ($p<0.05$) and distal oesophageal amplitude ($p<0.01$), higher prevalence of hiatal hernia ($p<0.01$) and increased prevalence of ineffective oesophageal motility ($p<0.01$). Patients with EO and BO had a significantly lower percentage of complete bolus transit compared to NERD and FH ($p<0.01$). Overall, abnormal bolus transit (ABT) for liquid swallows was found in 12% of FH, 20% of NERD, 54% of EO and 56% of BO ($p<0.01$). Combined impedance-manometry showed abnormal oesophageal function in 4% of FH, 4% of NERD, 22% of EO and 21% of BO patients with normal oesophageal manometry.

Conclusions:

Oesophageal motility abnormalities increases in parallel with the severity of GORD from NERD to EO and BO. Bolus transit abnormalities in severe reflux disease underscores the importance of impaired oesophageal function in the development of mucosal injury.

INTRODUCTION :

Gastro-oesophageal reflux disease (GORD) is a chronic relapsing disorder including a variety of conditions ranging from non-erosive reflux disease (NERD), erosive oesophagitis (EO), peptic stricture, Barrett's oesophagus (BO) and adenocarcinoma (1). Recent studies documented that up to 70% of reflux patients have typical reflux symptoms in the absence of endoscopically visible oesophageal mucosal injuries, making NERD the most common form of reflux disease (2,3). While EO and BO are objectively identifiable with certainty, NERD patients are characterized by normal endoscopy and incorporate subgroups which differ significantly in terms of clinical manifestations, pathophysiological characteristics and response to therapy. We have recently proposed to identify endoscopy-negative patients with reflux from those with a functional disorder on the basis of oesophageal 24-hour impedance combined with pH-metry (MII-pH) and symptom association analysis (4,5).

Several factors have been implicated in the protection against abnormal reflux: the His angle, the competence of Lower Oesophageal Sphincter (LOS), the crural diaphragm, a normal thorax-abdomen pressure gradient and an adequate oesophageal motility. Impairment of one or more of these mechanisms favours the reflux of stomach and/or duodenal contents into the oesophagus leading to symptoms and/or lesions (6). Previous studies have shown that impaired oesophageal motility leads to abnormal oesophageal clearance of the refluxed gastric content (7,8). Ineffective oesophageal motility (IOM), which is characterized by an increased number of low-amplitude contractions, is one of the most common types of dysmotility (9). In GORD patients, IOM has been associated with severe reflux episodes, worse symptoms and impaired oesophageal clearance with consequent prolonged acid exposure of the distal oesophagus (10). It has been reported that NERD patients have less severe reflux episodes and a much lower incidence of motility abnormalities than patients with erosive oesophagitis (EO) (11,12); however, other studies did not confirm the existence of significant differences between the two groups, regarding both reflux patterns and motility abnormalities (13-17). Therefore, data comparing motility abnormalities in patients with NERD and ERD are not conclusive. We suspect that these discrepancies are due to the difficulty to identify NERD patients and those with functional heartburn among the pool of endoscopy-negative patients. Moreover, there are few studies comparing the main manometric features and motility patterns in large groups of patients presenting all phenotypic manifestations of GORD.

Combined multichannel intraluminal impedance and oesophageal manometry (MII-EM) is considered an advanced tool for oesophageal function testing, since it provides simultaneous evaluation of oesophageal contractions and bolus transit and this reveals the

Savarino E, Gemignani L et al. - *Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH*

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4 functional aspects of oesophageal motility (18). Normal values for oesophageal clearance
5 assessed by combined impedance-manometry have been previously reported by Tutuian et al.
6 (19). Given the recent application of this technique in clinical setting, information about the
7 characteristics of bolus transport in patients with various forms of GORD are still lacking
8 (17,20).
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12 The primary aim of the present study was to compare the manometric features and
13 motility patterns in well-defined subgroups of GORD, subclassified by means of endoscopy
14 and/or impedance-pH monitoring. A secondary aim was to assess whether differences exist in
15 terms of functional aspects of oesophageal motility among the various subsets of reflux
16 patients by means of MII-EM.
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METHODS :

Subjects

In this retrospective analysis of prospectively collected data we included patients with typical GORD symptoms (*e.g.*, heartburn and regurgitation), lasting for more than 6 months and occurring at least three times weekly, presenting to the GI motility centre at the University Hospital of Genoa, Italy. Exclusion criteria were: history of thoracic, oesophageal, or gastric surgery; primary or secondary severe oesophageal motility disorders (*e.g.*, achalasia, scleroderma, diabetes mellitus, autonomic or peripheral neuropathy, myopathy); underlying psychiatric illness; history of alcohol or drug abuse; evidence of erosive oesophagitis at previous (5 years) endoscopy in case of patients with NERD.

Previously collected data in 48 healthy volunteers [22 men, mean age 44 years (range 22-77), mean BMI 23 Kg/m² (16-34)] without any type of digestive and systemic symptoms were used as normal values. The study protocol was approved by the local Ethics Committee and performed according to the Declaration of Helsinki. All patients provided written informed consent to use collected data before their data were used in this study.

Study Protocol

All subjects underwent physical and clinical examination and a detailed medical history (including current medication, height and weight for the calculation of their Body Mass Index (BMI), tobacco use, alcohol and coffee consumption), oesophageal manometry and upper GI endoscopy to assess the presence or not of oesophageal mucosal injury. Based on the results of upper endoscopy, patients were then subdivided into three major groups: a) EO, in case of presence of visible lesions of the oesophageal mucosa and graded according to Los Angeles Classification (21); enrolled patients with erosive oesophagitis underwent a further upper endoscopy after 8-14 weeks of high dose proton pump inhibitor (PPI) therapy to exclude the presence of intestinal metaplasia under their ulcerated mucosa; b) BO in case of histological detection of specialized intestinal metaplasia on four-quadrant biopsy specimens taken at 1-cm intervals above the gastro-oesophageal junction or the proximal margin of gastric folds in case of hiatal hernia (5); c) endoscopy-negative in case of absence of oesophageal mucosal breaks, on the basis of Montreal Classification (22). Within 1-5 days (median 3 days) of upper endoscopy, endoscopy-negative patients underwent 24-hour oesophageal MII-pH monitoring off-PPI therapy. Patients treated with antisecretory drugs had been asked to discontinue acid suppressive therapy at least 30 days before the examination. During the wash-out period, patients were allowed to use an oral antacid or alginate on as-

needed basis for the relief of heartburn. Endoscopy-negative patients were classified based on the results of impedance-pH testing with symptom association probability analysis (SAP), as follows: patients were considered to have NERD in case of abnormal oesophageal acid exposure time (AET) and in case of normal AET with positive SAP ($\geq 95\%$) and SI ($\geq 50\%$) for acid and/or non-acid refluxes (23); patients were classified as having functional heartburn (FH) if they had normal endoscopy, normal distal oesophageal acid exposure on 24-h impedance-pH monitoring and negative symptom association analysis (4,5). NERD patients examined with oesophageal pH-metry only were excluded from the study.

Oesophageal Conventional and Impedance Manometry testing

Patients were asked to discontinue any medication that would influence oesophageal motor function at least one week before performing tests of oesophageal function. From 2003 to 2007 each patient underwent oesophageal function testing by means of conventional manometry using an eight-lumen, water-perfused, oesophageal manometry catheter (Mui Scientific, Canada) assembly consisting of four radial ports and four lateral ports spaced 5 cm apart and radially orientated 120° with respect to each other. Moreover, from 2007 to 2010, each patient underwent oesophageal function testing by means of MII-EM using a Koenigsberg 9-channel probe (Sandhill oesophageal function testing [EFT] catheter; Sandhill Scientific Inc, Highlands Ranch, CO). The 4.5-mm diameter catheter design has 2 circumferential solid-state pressure sensors at 5 and 10 cm from the tip and 3 unidirectional solid-state pressure sensors at 15, 20, and 25 cm. Impedance measuring segments, consisting of 2 rings placed 2 cm apart, centered 10, 15, 20, and 25 cm from the tip. The methodology of catheter placement, patient instruction and performance has been previously described for both techniques (24-27). Manometric parameters used to characterize swallows included: (1) contraction amplitude 5 and 10 cm above the LOS, (2) distal oesophageal amplitude (DEA) as the average of contraction amplitude 5 and 10 cm above the LOS, and (3) onset velocity of oesophageal contractions in the distal part of the oesophagus (i.e., contraction velocity between 10 and 5 cm above the LOS). Mid-respiratory resting pressure and LOS residual pressure during swallowing were used to assess LOS function. The MII parameters we analyzed included bolus entry at each specific level obtained at the 50% point between 3-sec pre-swallow impedance baseline and impedance nadir during bolus presence and bolus exit determined as return to this 50% point on the impedance recovery curve (19).

Swallows were classified by manometry as: (1) normal if contraction amplitudes 5 and 10 cm above the LOS were each ≥ 30 mm Hg and distal onset velocity was < 8 cm/s, (2)

Savarino E, Gemignani L et al. - *Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH*

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4 ineffective if either of the contraction amplitudes 5 and 10 cm above the LOS was <30 mm
5 Hg, or (3) simultaneous if contraction amplitudes 5 and 10 cm above the LOS were each ≥ 30
6 mm Hg and distal onset velocity was >8 cm/s. Diagnoses of manometric motility
7 abnormalities were established by using international criteria and considering only saline
8 swallows (9) as follows: a) Ineffective Oesophageal Motility (IOM) was defined as $\geq 30\%$
9 saline swallows with contraction amplitude <30 mm Hg in either 1 of the 2 distal sites located
10 5 and 10 cm above the LOS; b) Diffuse Oesophageal Spasm (DOS) defined as 20% or more
11 simultaneous contractions; c) Nutcracker Oesophagus (NO) defined as normal peristalsis of
12 the oesophageal body with an average DEA exceeding 180 mmHg; d) Normal Peristalsis
13 (NP), defined as not more than 20% ineffective and not more than 10% simultaneous
14 swallows with DEA < 180mmHg and with normal LOS resting and residual pressures.
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17 Swallows were classified by MII as showing: (1) complete bolus transit if bolus entry
18 occurred at the most proximal site (20 cm above the LOS) and bolus exit points were recorded
19 in all 3 distal impedance measuring sites (i.e., 15, 10, and 5 cm above the LOS), and (2)
20 incomplete bolus transit if bolus exit was not identified at any of the 3 distal impedance
21 measuring sites. Overall diagnosis of oesophageal transit abnormalities was defined as normal
22 liquid transit if at least 80% of liquid swallows had complete bolus transit and normal viscous
23 transit if at least 70% of viscous swallows had complete bolus transit. Conversely, abnormal
24 liquid transit is defined as $\geq 30\%$ liquid swallows having incomplete bolus transit and
25 abnormal viscous transit as $\geq 40\%$ viscous swallows having incomplete viscous swallows (19).
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40 **Oesophageal impedance and pH monitoring**

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42 Oesophageal impedance-pH monitoring was performed using an ambulatory multi-
43 channel intraluminal impedance and pH monitoring system (Sleuth[®], Sandhill Scientific, Inc.,
44 Highland Ranch, CO). The system included a portable data logger with impedance-pH
45 amplifiers and a catheter with one antimony pH electrode and eight impedance electrodes at 2,
46 4, 6, 8, 10, 14, 16, and 18 cm from the tip of the catheter. Each pair of adjacent electrodes
47 represented an impedance-measuring segment (2 cm length) corresponding to one recording
48 channel. The six impedance and one pH signals were recorded at 50 Hz on a 128 MB
49 CompactFlash (SanDisk, Milpitas, California, US). The methodology of probe calibration,
50 catheter placement, patient instruction and performance has been previously described (4,5).
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52 On the monitoring day, each subject ate three standard meals of a Mediterranean diet, as
53 previously reported (28).
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4 Definitions of reflux episodes, parameters of gastro-oesophageal reflux and symptom
5 association analysis are described in previous publications (4,23).
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8 **Statistical analysis**

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10 Differences in proportions were compared using the chi-square or Fisher's exact test,
11 depending on the sample size. Unless otherwise specified, data are presented as mean and
12 range values. Since data were not normally distributed, differences between groups were
13 compared using Kruskal-Wallis and/or Mann-Whitney tests. **Multi-nominal logistic**
14 **regression using gender and endoscopic finding as factors and age as covariant was employed**
15 **to test the likelihood of potential confounders on the differences in manometric abnormalities.**
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17 Differences were considered statistically significant when $p < 0.05$.
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RESULTS:

Seven hundred and ninety-eight consecutive patients (412 female, mean age 51, range 18-88) with typical symptoms of GORD met the enrolment criteria and entered the study. During upper endoscopy, we identified 340 patients (171 F, mean age 49, range 21-87) with EO, 352 without mucosal breaks (201 F, mean age 49, range 18-78) and 106 (40 F, mean age 58, 21-87) patients had histologically confirmed Barrett oesophagus. In the EO group, 199 patients had grade A and 82 had grade B, 39 had grade C and 20 had grade D oesophagitis. During the impedance-pH monitoring period of endoscopy-negative patients, 309 (186 F, mean age 49, range 18-78) reported at least one type of typical gastroesophageal reflux symptom (i.e., heartburn and regurgitation) and were included in the final analysis. Among them, 213 were classified as having NERD, whereas 96 patients were identified as having FH. Finally, 48 healthy volunteers (27F, mean age 44, range 22-77) were enrolled, and underwent oesophageal manometry and 24h pH-MII testing, as well as upper endoscopy.

Detailed demographic features of all patients and HVs are shown in **Table 1**. Patients with BO and EO were more frequently male (62% vs.50% vs. 41% Vs. 38%, $P<0.01$) and had a higher mean body mass index (BMI) compared to those with NERD and FH (27 vs. 26,4 vs. 25.2% Vs. 23%, $P<0.01$). Moreover, patients with BO were more frequently smokers than those of other subgroup (38% vs. 22% vs. 19% vs. 26%, $P<0.01$) and they tended to consume alcohol more often (55% vs. 41% vs. 43% vs. 38%, $P=NS$) but statistical significance was not reached. No differences among these groups were found with regard to mean age and coffee consumption. The HVs control group had similar demographic (27 females; mean age 44 years; range 22–71 years) and body mass index (BMI 23 kg/m²; range 18–34 kg/m²) characteristics compared to reflux patients.

OESOPHAGEAL PERISTALSIS EVALUATED BY OESOPHAGEAL MANOMETRY

Manometric findings regarding mean LOS resting pressure, distal oesophageal waves amplitude (DEA) and prevalence of hiatal hernia, are shown in **Table 2**. Mean LOS resting pressure was not different between the controls and patients with FH, but decreased in relation to the progressive severity of GORD, with EO and BO patients having the lowest values ($p <0.01$). Also the mean DEA was similar in patients with FH and HVs, but decreased significantly in patients with NERD ($p<0.05$) and in those with EO and BO ($p<0.01$). Hiatal hernia prevalence was higher in patients with BO compared to the other subgroups ($p>0.01$). The same was true for patients with EO compared to NERD, FH and HVs ($p<0.01$). Finally, patients with NERD had more frequently a hiatal hernia than patients with FH and HVs

Savarino E, Gemignani L et al. - Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH

($p < 0.01$). No differences have been observed regarding onset velocity of contractions, LOS relaxation duration and UES pressure ($p = ns$).

Figure 1 illustrates the different motility patterns among the various groups of patients. For the purpose of this study DES and Nutcracker Oesophagus were considered together (DES/NE). Moreover, the final manometric diagnosis for each patient was based on the liquid swallows to remain consistent with current tradition. Prevalence of IOM was statistically higher ($p < 0.01$) in patients with mucosal lesions than in the other groups, occurring in 42% of patients with BO and in 38% of patients with EO, compared to 19% of NERD patients, 8% of FH and 4% of HVs. Patients with NERD had more frequently IOM than those with FH and HVs ($p < 0.01$). Normal peristalsis was found more in HVs and FH than the other subgroups ($p < 0.01$). No differences were found in terms of DES/NE prevalence among the various subgroups ($p = ns$).

OEESOPHAGEAL BOLUS TRANSIT ASSESSED BY MULTICHANNEL INTRALUMINAL IMPEDANCE

Results are summarized in **Figure 2a and b**. Oesophageal bolus transit was assessed in 260 patients (48 FH, 113 NERD, 65 EO and 34 BO) for liquid swallows and in 151 patients (31 FH, 66 NERD, 33 EO and 21 BO) for viscous swallows. Patients with EO and BO had a significantly lower percentage of complete bolus transit compared to NERD and FH ($p < 0.01$). Six patients with FH (6/48), 23 with NERD (23/113), 35 with EO (35/65) and 19 (19/34) with BO had abnormal bolus transit (ABT) with liquid swallows ($p < 0.01$), while 5 with FH (5/31), 15 with NERD (15/66), 18 with EO (18/33) and 12 (12/21) with BO had ABT with viscous swallows ($p < 0.01$). In addition, patients with EO and BO had a significant increase in TBTT (8.7 s, liquid; 8.9 s, viscous and 9.1 s, liquid; 9.6 s, viscous, respectively) compared to NERD (6.8 s, liquid; 7.7 s, viscous) and FH controls (6.8 s, liquid; 7.3 s, viscous) ($p < 0.05$) with both liquid and viscous swallows.

The multi-nominal regression analysis found no significant ($p = 0.196$) effect of gender distribution but a significant ($p < 0.001$) co-variation of age on the distribution of manometric abnormalities in patients with various endoscopic findings. Of note is that age didn't differ across various endoscopic findings (Table 1) and the age difference between patients with normal manometry (47.0 ± 0.7 years), ineffective oesophageal motility (54.7 ± 0.9 years) and distal oesophageal spasms (51.9 ± 1.4 years), albeit being statistically significant ($p < 0.001$), is most likely clinically non-relevant.

Savarino E, Gemignani L et al. - Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH

COMBINED IMPEDANCE-MANOMETRY FINDINGS

Bolus transit for liquid swallows in relation to the manometric findings is shown in **Figure 3**. Combined MII-EM information for liquid swallows revealed that out of all patients with IOM, 63% of EO patients and 67% of BO patients had ABT versus 50% of NERD and 29% of FH ($p<0.05$). Of all patients with DOS, the frequency of ABT was similar in all subgroups (60% EO vs. 57% BO vs. 46% NERD vs. 50% FH, $p=ns$). Considering all patients with normal peristalsis, 45% of EO and 47% of BO patients had ABT versus 5% of NERD and 5% of FH ($p<0.01$). Similar results were observed evaluating bolus transit for viscous swallows, as illustrated in **Figure 4**. Of all patients with IOM, 67% of EO patients and 57% of BO patients had ABT versus 41% of NERD and 25% of FH ($p<0.05$). Of all patients with DOS, the frequency of ABT was similar in all subgroups (50% EO vs. 60% BO vs. 56% NERD vs. 67% FH, $p=ns$). Considering all patients with normal peristalsis, 50% of EO and 56% of BO patients had ABT versus 7% of NERD and 8% of FH ($p<0.01$). Overall, combined impedance manometry showed an oesophageal motility abnormality in 4% of FH, 4% of NERD, 22% of EO and 21% of BO patients in whom conventional manometry alone would have reported a normal motility peristaltic profile (**Figure 5**).

DISCUSSION:

In the present study, the retrospective analysis of prospectively collected data in a large group of unselected GORD patients, accurately classified by means of upper endoscopy, oesophageal biopsies and impedance-pH findings, supports earlier results (11,25) that with increasing severity of mucosal damage there is an increase of manometric abnormalities findings. However, in contrast with previous investigations (14-17), we observed that there is an increase of IOM prevalence as the degree of mucosal lesions become worse. Indeed, we found that IOM was the most common motility abnormality in all patients with GORD and its prevalence gradually increased on passing from NERD to EO and BO, while patients with FH and HVs had a much lower frequency of this alteration, thus supporting the exclusion of FH patients from the realm of GORD in agreement with Rome III criteria (29). We have hypothesized that the so far inconclusive data in previous studies regarding this issue were mainly due to the difficulty to clearly separate patients with NERD from the functional population (14-17). Moreover, as novel finding, we observed that oesophageal clearing function, assessed by means of MII-EM, decreased as the severity of mucosal damage increased, with EO and BO patients having the greatest prevalence of abnormal bolus transit pattern. Interestingly, in contrast with NERD and FH patients, abnormal bolus transit was found also in case of normal motility and not only in case of IOM or DOS/NO, as one could expect. Therefore, combined impedance manometry permits to observe an impairment of oesophageal function in patients with GORD, despite a normal peristaltic profile reported by conventional manometry. This suggests that in severe reflux disease patients the impaired oesophageal clearance may be due to failure of primary peristalsis – IOM - or reduced capacity to transport along the oesophagus – abnormal bolus transit –.

In the current study, we confirmed data obtained by Frazzoni et al (25), who demonstrated that patients with reflux disease have a greater prevalence of manometric abnormalities in terms of lower LOS resting pressure, lower distal oesophageal wave amplitude and higher prevalence of hiatal hernia than those with FH and controls. In agreement with Wu et al. (12), the frequency of these abnormalities gradually increases from NERD to EO and also to BO (24), while there was no difference between EO and BO. In contrast, our manometric findings are at variance with those observed in recent investigations (14-16), where no significant differences were found between NERD and EO. However, the above Authors defined NERD patients on the sole basis of a negative upper endoscopy and abnormal pH-testing or presence of symptom-reflux relationship in patients with abnormal

Savarino E, Gemignani L et al. - *Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH*

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4 pH-metry in order to exclude FH patients. This carries the risk of ruling out patients with
5 normal pH and positive symptom-reflux association to acid and non-acid reflux, who
6 represent a significant part of NERD, as shown by several studies (4,5,30-32). Moreover,
7 according to Wu et al. (12) and in contrast with other investigations (16,17) we found that
8 patients with reflux disease have a greater prevalence of IOM than those with FH and
9 controls, and that IOM gradually increases from NERD to EO to BO. Again the discrepancies
10 of these results were mainly due to the unclear separation among the different entities of
11 GORD, with the possible inclusion of patients with FH and exclusion of patients with Non-
12 Acid Reflux Disease.
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20 As to the assessment of bolus transit patterns in patients with various degree of reflux
21 disease, to the best of our knowledge, only two studies have been published (17,20) regarding
22 this issue. Domingues et al. (20) evaluated 25 patients with mild GORD – 22 with grade A-B
23 EO and 3 with NERD – and they found that GORD patients had a delayed bolus transport
24 compared to controls, although normal bolus transport was observed in the majority of the
25 swallows (91% of liquid and 81% of viscous swallows). Similarly, Chen et al. (17) noted no
26 difference in the prevalence of complete bolus transport in 20 NERD patients compared with
27 controls, while 20 patients with EO exhibited an increase in the frequency of incomplete
28 bolus transit, which was also accompanied by more prolonged bolus transit. However, these
29 studies have several limitations, mainly related to the small sample size, the enrolment of
30 patients with only EO or NERD and finally the correct identification of NERD patients.
31 Indeed, Chen et al. defined NERD only by means of endoscopically undetectable mucosal
32 lesions with the consequent risk to include patients with FH in this group, while Domingues et
33 al. included only 3 NERD patients and identified them only on the basis of an abnormal
34 oesophageal acid exposure. Instead, in the current study evaluating a large population of well
35 defined GORD patients using MII-pH, we found that the oesophageal clearing function
36 decreased as the severity of mucosal damage increased, with EO and BO patients having the
37 greatest prevalence of abnormal bolus transit pattern. This impairment was evident in case of
38 both liquid and viscous swallows. Moreover, they had a significant delayed bolus transport
39 compared to NERD and FH. Interestingly, patients with more severe reflux disease presented
40 an abnormal bolus transit pattern also in case of normal motility and not only in case of IOM
41 or DOS/NO, as observed in patients with NERD and FH. Therefore, in these patients the
42 defect of oesophageal motility is more severe than the simple peristaltic profile one can assess
43 by conventional manometry, thus underlying the importance of oesophageal clearance
44 evaluation by means of MII-EM in them.
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Several hypotheses may explain the increased prevalence of IOM and the abnormal bolus transit patterns in patients with more severe reflux disease. First, it could be partly related to a severe oesophageal mucosal inflammation induced by increased gastro-oesophageal reflux, which determines a reduction in oesophageal compliance and an increased resistance during bolus movement with a consequent delayed bolus transport. Moreover, it has been recently demonstrated that the rate of triggering secondary peristalsis in patients with NERD is significantly lower than in normal subjects (33). The same phenomenon may be also present in patients with severe reflux disease causing a delay or stop during bolus transport. Different patterns could be also explained by the difference in oesophageal tone noted in severe GORD patients compared to those with mild GORD (34). Also oesophageal abnormalities represented by different traction force or oesophageal shortening have been taken into consideration (35-37). Anyway, our results suggest that the peristaltic amplitude alone does not explain the rate of incomplete bolus transit and that other mechanisms are involved in determining incomplete bolus transit in patients with oesophageal mucosal injuries.

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As to the limitations of our study, the 30 day washout period before the upper endoscopy in patients using acid suppressive medication could be considered as too short for lesions to develop. Still, in our experience, this represents the maximum we can ask to patients in order to obtain good compliance and without them dropping out from the study. Moreover, the incidence of recurring erosive lesions after a shorter period of PPI cessation remains unknown.

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In conclusion, this study shows that identifying with accuracy – i.e. upper endoscopy and impedance-pH monitoring – GORD patients from those with functional disease leads to show relevant differences in terms of oesophageal manometric features, motility and bolus transit patterns, therefore clarifying the discrepancies observed in earlier studies. We demonstrate that increasing degrees of oesophageal mucosal damage is associated with a progressively more severe deflection of oesophageal function, expressed by an increased frequency of IOM and abnormal bolus transit patterns. This seems to reveal a novel piece of the puzzle related to the development of oesophageal mucosal injury.

The authors declared no conflict of interest.

Savarino E, Gemignani L et al. - *Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH*

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Savarino E, Gemignani L et al. - *Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH*

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Savarino E, Gemignani L et al. - Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH

Table 1. Demographic parameters of overall GORD patients (n=755) and HV (n=48)

<i>Demographics parameters</i>	HV	FH	NERD	EO	BO	<i>p Value</i>
Patients, n	48	96	213	340	106	
Female patients, n (%)	27 (56%)	60 (62%)	126 (59%)	171 (50%)	40 (38%)	p <0.01
Mean Age (range), y	44 (22-77)	48 (18-76)	49 (20-84)	49 (21-87)	58 (21-87)	ns
Mean BMI (range), kg/m²	23 (16-34)	23 (16-34)	25.2 (18-48)	26.4 (16-48)	27 (18-39)	p <0.01
Alcohol consumption, n (%)	22 (46%)	36 (38%)	91 (43%)	138 (41%)	58 (55%)	ns
Coffee consumption, n (%)	36 (75%)	65 (68%)	161 (76%)	218 (64%)	78 (74%)	ns
Smoke, n (%)	14 (29%)	25 (26%)	40 (19%)	75 (22%)	40 (38%)	p <0.01

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Table 2. Manometric features in GORD patients (n=755) and HV (n=48)

<i>Population</i>	Mean LOS Tone, mmHg (range)	Mean DOA, mmHg (range)	Hiatal Hernia, n (%)
Healthy Volunteers (n=48)	27.6 (12-44) [#]	101.6 (24.2-211.8) [#]	7 (15%) [#]
Functional Heartburn (n=96)	26.1 (9-42) [#]	94.4 (20.1-198) [#]	32 (33%) [#]
NERD (n =213)	20 (3-44) ^{&}	79 (22.1-193.1) ^{&}	124 (58%) ^{&}
Erosive Oesophagitis (n=340)	15.4 (1-43) [*]	49.2 (14.1-188-3) [*]	238 (70%) [*]
Barrett Oesophagus (n=106)	13 (1-39) [*]	41.2 (12-231.8) [*]	87 (82%) [*]

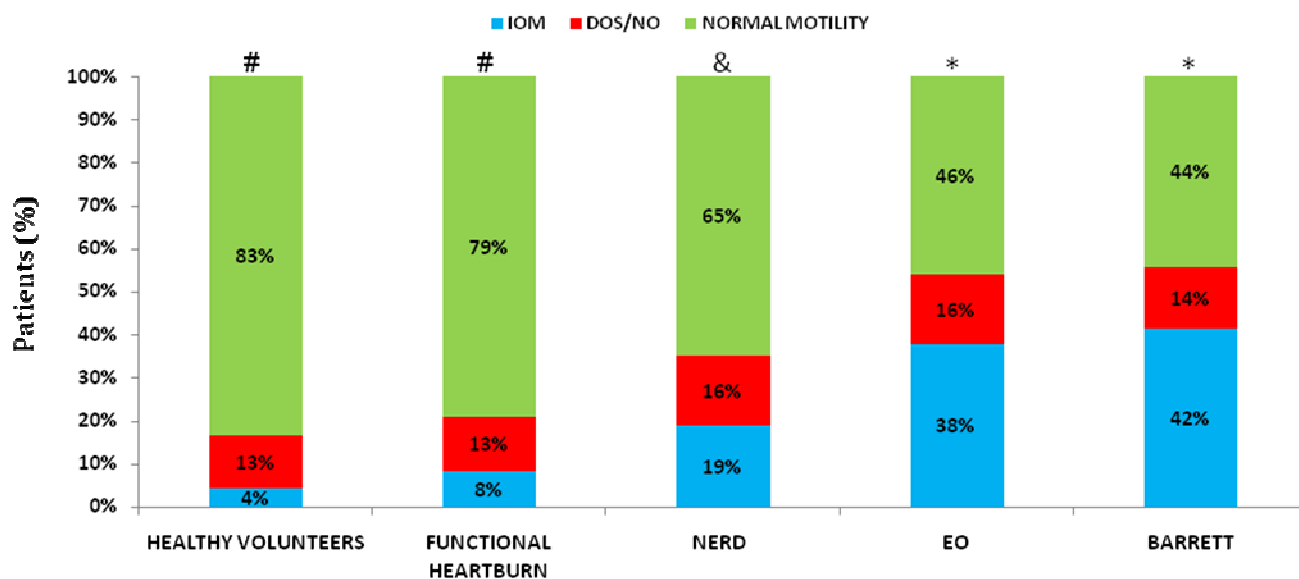
[#] p<0.05 vs. NERD, EO and BO

[&] p<0.05 vs. BO, EO, FH and HV

^{*} p<0.05 vs. NERD, FH and HV

Savarino E, Gemignani L et al. - Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH

Figure 1. Manometric patterns in GORD patients (n=755) and HV (n=48)



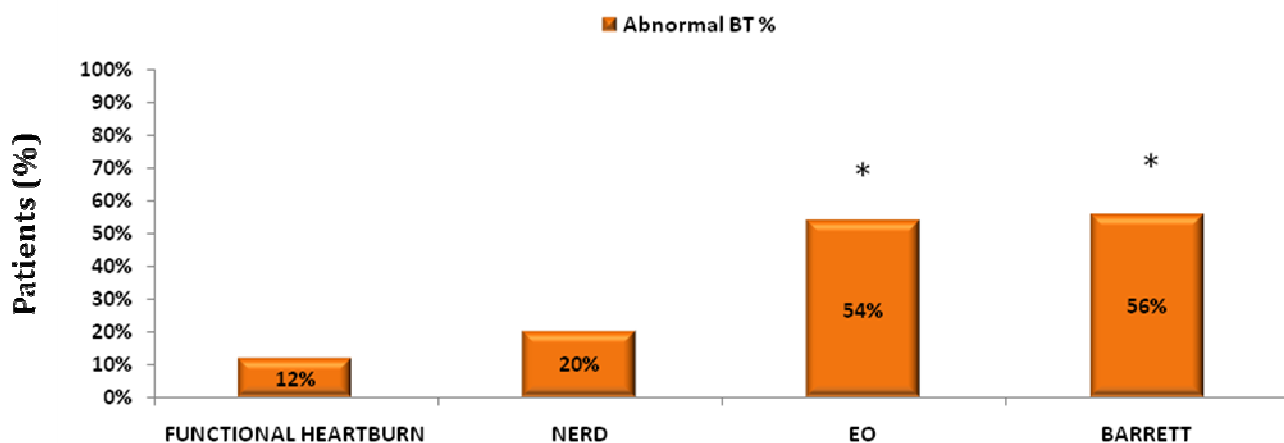
$p < 0.05$ vs. NERD, EE and BE

& $p < 0.05$ vs. BE, EE, FH and HV

* $p < 0.05$ vs. NERD, FH and HV

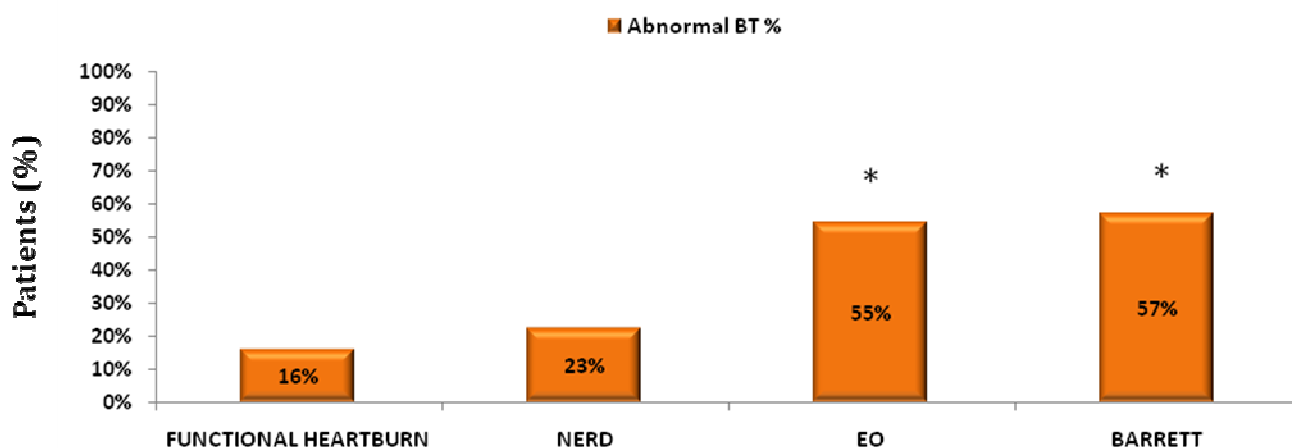
Figure 2. Abnormal Bolus Transit Diagnosis in the various subgroups of GORD patients (n=260) for liquid swallows (2a) and viscous swallows (2b)

2a. Liquid Swallows



* p<0.01 vs. NERD and FH

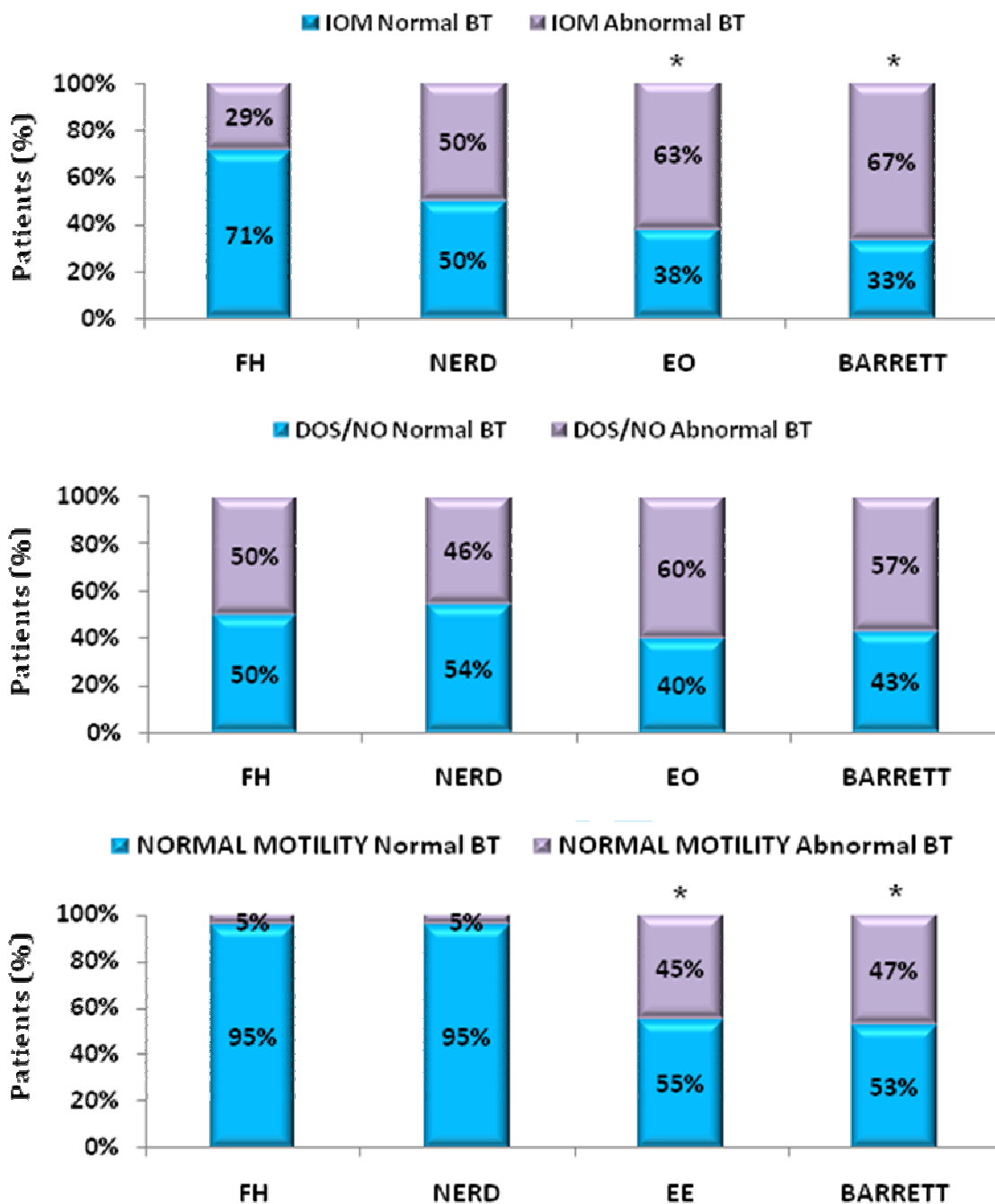
2b. Viscous swallows



* p<0.01 vs. NERD and FH

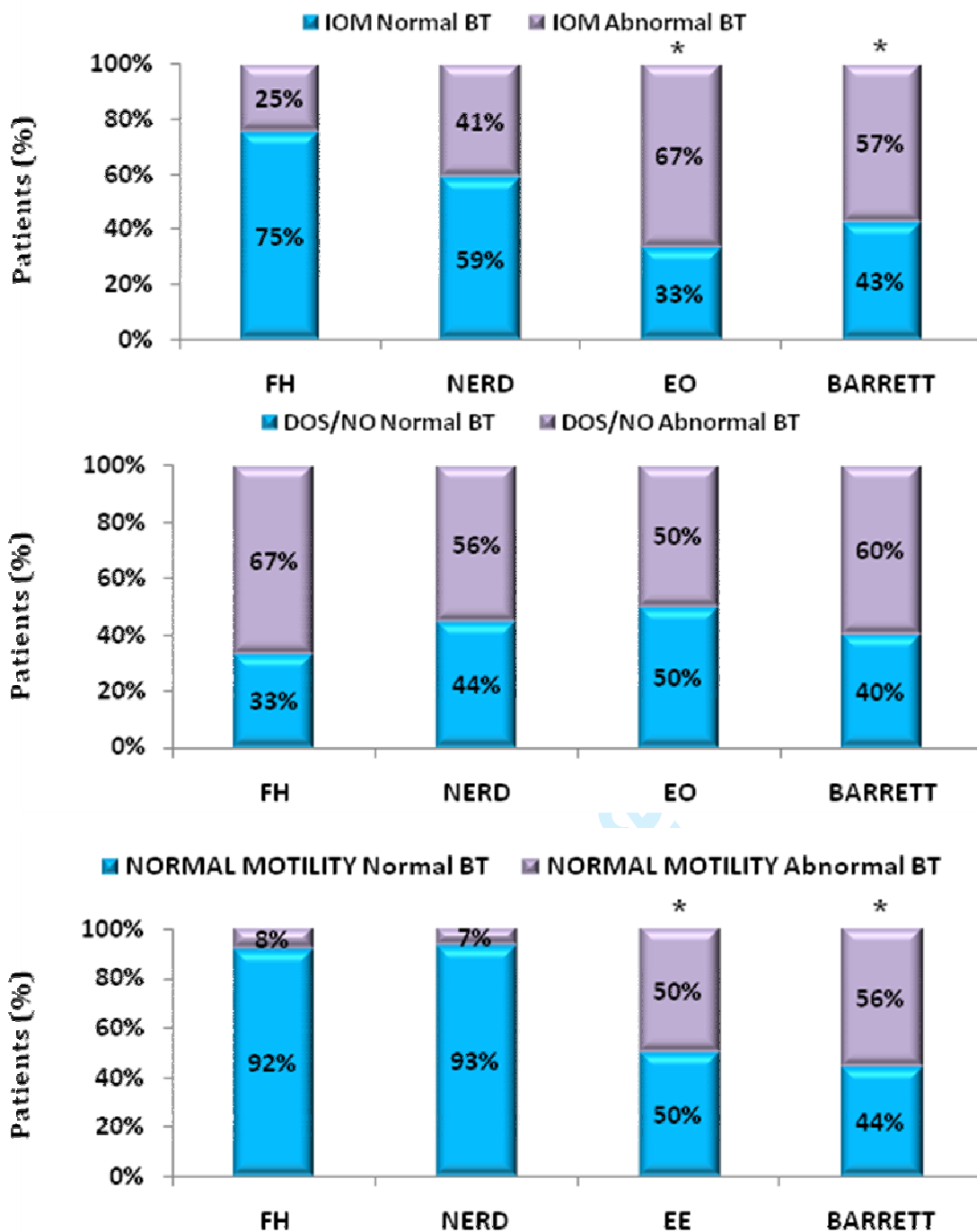
Savarino E, Gemignani L et al. - Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH

Figure 3. Bolus Transit Diagnosis in the various subgroups of GORD patients (n=260) in relationship to the manometric diagnosis for liquid swallows



* p<0.05

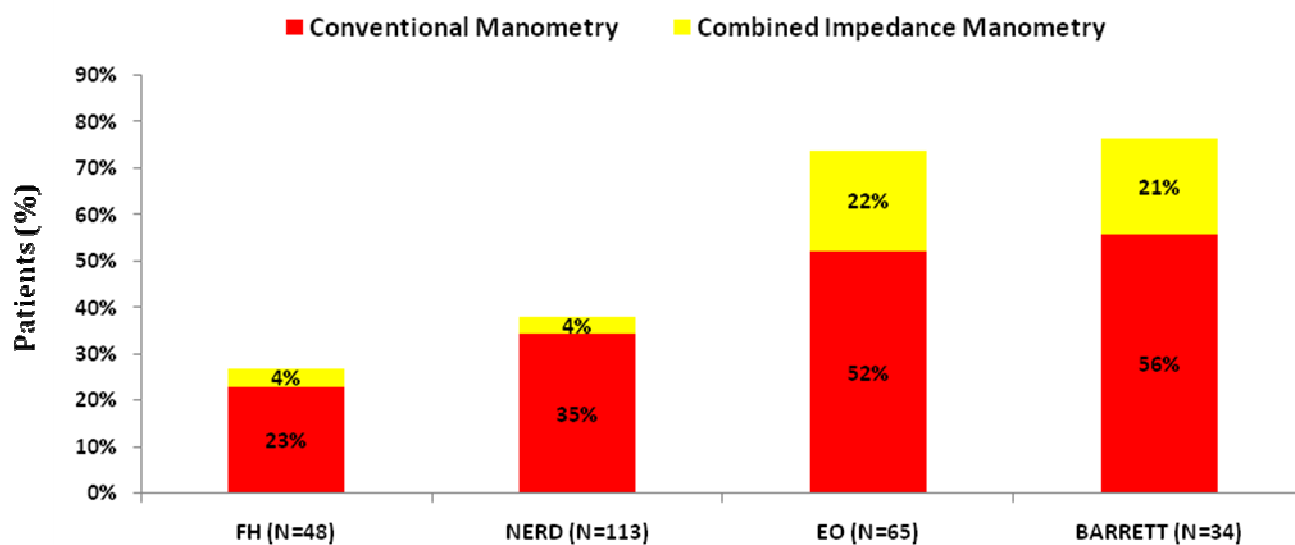
Figure 4. Bolus Transit Diagnosis in the various subgroups of GORD patients (n=260) in relationship to the manometric diagnosis for viscous swallows



* p<0.05

Savarino E, Gemignani L et al. - *Prevalence of esophageal motility abnormalities in patients with EE, BE, NERD and FH*

Figure 5. Added value of combined impedance manometry testing compared with conventional manometry alone.



STATEMENTS:

A: Guarantor of this paper: Edoardo Savarino, MD, PhD; Vincenzo Savarino, MD

B: Authors contribution:

- Edoardo Savarino, MD: design of the study, data collection and analysis, writing of the manuscript, approving final version.
- Lorenzo Gemignani, MD: data collection and analysis, writing of the manuscript, approving final version.
- Daniel Pohl, MD: writing of the manuscript, approving final version
- Patrizia Zentilin, MD: design of the study, data collection and analysis, approving final version.
- Pietro Dulbecco, MD: design of the study, data collection and analysis, approving final version.
- Lorenzo Assandri, MD: data analysis, writing of the manuscript, approving final version.
- Elisa Marabotto, MD: data collection and analysis, approving final version.
- Daria Bonfanti, MD: data collection and analysis, approving final version.
- Simona Inferrera, MD: data collection and analysis, approving final version.
- Valentina Fazio, MD: data collection and analysis, approving final version.
- Alberto Malesci, MD: writing of the manuscript, approving final version
- Radu Tutuian, MD: writing of the manuscript, approving final version
- Vincenzo Savarino, MD: design of the study, data collection and analysis, writing of the manuscript, approving final version.

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D: Potential competing interests: none