

Screening of Minor Disorders of Peristalsis of Esophagus in Iranian Patients with Nonerosive Reflux Disease (NERD) Based on 24-Hour Multichannel Intraluminal Impedance-pH (MII-PH) Monitoring Tests

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Abstract

Background/Aims: Impedance associated with PH monitoring is a new technique that can be used to detect acidic, weakly acidic, and nonacidic reflux episodes. Also, this technique can be used to recognize fluids and gas. The present study was conducted to evaluate the differences in the total number of reflux episodes and its composition in participants with nonerosive reflux disease (NERD) and minor disorders of peristalsis of esophagus and NERD based on the new technique of combined multichannel intraluminal impedance-pH(MII-PH) monitoring in Iranian population.

Method: This study was conducted on 1134 participants aged 18 to 70 years with NERD. They were selected using a questionnaire and esophagogastroduodenoscopy findings. MII-pH monitoring test was performed for all the patients. The number of reflux episodes and its composition, DeMeester score, integrated relaxation pressure 4 (IRP4), and distal contractile integral (DCI) were recorded.

Results: Of the 325 participants in the ineffective esophageal motility group, 66.7% showed a pathological acid exposure of time (EAET), which was more than the normal peristalsis group (43.6%). The frequency of upright and supine position of acid reflux was both 51.1% in ineffective esophageal motility (IEM) participants, whereas the frequency of upright and supine position of acid reflux in patients with normal peristalsis was 24.8% and 23.1%, respectively. Weakly acid reflux was more prevalent in NERD participants with IEM than participants with normal peristalsis.

Conclusion: The present study revealed that acid, weakly acid, and gas reflux were more prevalent in NERD participants with minor disorders of peristalsis of esophagus than in patients with normal peristalsis. Mean integrated relaxation pressure 4 (IRP4) and distal contractile integral (DCI) were significantly lower in those with minor disorders of peristalsis of esophagus than in those with normal peristalsis.

Keywords: Minor Disorders Peristalsis of Esophagus, NERD, GERD, MII-pH,

1. Introduction

Minor disorders of peristalsis of esophagus is a type of hierarchical analysis of esophageal manometry based on the most recent Chicago Classification that include ineffective esophageal motility (IEM) and fragmented peristalsis (FP) (Rohof & Bredenoord, 2017). Impedance associated with PH monitoring is a new technique that can be used to detect acidic, weakly acidic, and nonacidic reflux episodes and recognize fluids and gas (Bredenoord, 2008). High-resolution manometry (HRM) is now considered the gold standard for the diagnosis of esophageal motility disorders. Chicago Classification is a standardized approach for the analysis and diagnosis of esophageal motility disorders and improves our knowledge of pathophysiology and upgrade the management of motility disorders and gastroesophageal reflux disease (Rohof & Bredenoord, 2017). Several factors, such as integration relaxation pressure 4 (IRP4) of lower esophageal sphincter, esophageal body contraction, and gastric juice, are associated with esophageal symptoms and mucosal injuries (Frazzoni et al., 2013; Tack & Pandolfino, 2018). Kahrilas et al. reported that

peristaltic dysfunction, defined as failed or hypotensive primary peristalsis, occurs in 25% to 48% of oesophagitis cases. Also, Diener et al. showed that severe IEM disorders are associated with more severe gastroesophageal reflux disease (GERD) presentation (Savarino et al., 2013). In recent studies, the latest version of the Chicago Classification (v 3) was directly compared to the previous version and researchers reported that minor disorders of peristalsis of esophagus were diagnosed significantly less often by the latest version, and these patterns were more often classified as normal in symptomatic patients (Rohof & Bredenoord, 2017). Thus, significance of the relationship between minor disorders of peristalsis of esophagus and GERD is questionable. NERD is characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions or breaks in conventional endoscopy. It has been estimated that the prevalence of NERD in those part of the population with reflux is 60% to 71.9% (Savarino et al., 2013; Yaseri, 2018). The present study was conducted to prospectively evaluate the differences in the total number of reflux episodes and its composition in patients with minor disorders of esophageal peristalsis and NERD based on the new technique of combined multichannel intraluminal impedance-pH(MII-PH) monitoring in Iranian population.

2. Materials and Methods

Patients:

The study population was selected from all patients who had gastroesophageal reflux disease symptoms (heartburn and regurgitation) at least twice a week and who were admitted to Firoozgar hospital in Tehran, Iran. GERD questionnaire was used as the study tool. All participants provided informed consent and accepted to complete the standard form of GERD questionnaire. Diagnosis was based on questionnaires and results of esophagogastroduodenoscopy (EGD). In this study, 1635 participants with no underlying diseases who had GERD symptoms for at least 3 months were initially selected. Of the patients, 70.2% (1148/1635) appeared normal in EGD and were considered to have non- erosive gastroesophageal disease (NERD). This case-control study was conducted on 1134 patients with NERD aged 18 to 70 years. The case group consisted of 325 NERD participants with IEM, and the control group included 809 NUD participants with normal peristalsis. The case and control groups had no history of documented ulcer, large hiatal hernia, esophageal varices, history of malignant diseases, previous foregut surgery, cardiovascular diseases, pregnancy, breastfeeding, psychiatric illness, and history of alcohol or drug abuse. Also, fragmented peristalsis and achalasia findings in esophageal manometry, EGD, or barium swallows were excluded. GERD symptoms (regurgitation and NCCP) and negative esophagitis in EGD were included. Body mass index (BMI) was calculated by weight in kilogram in fasting state divided by the square of height in meters. Smoking was recorded as positive or negative. Moreover, esophageal manometry and esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring tests were performed for all patients.

Esophageal Multichannel Intraluminal Impedance-pH (MII-PH) Monitoring:

Esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring was performed using an ambulatory MII-pH system (manufactured by Mui Scientific, Ontario, CA). The MII-PH catheter (Unisensor AG, Bahnstr, Switzerland), with 6 impedance electrodes and 1 pH sensor (K6011-EI-0632), was inserted transnasally. Impedance measuring sites were located in the distal esophagus at 3, 5, 7, and 9 cm and 2 impedance measuring sites in the proximal esophagus at 15 and 17 cm above the LES. One antimony pH sensor was located 5 cm above the LES. MII-PH data were recorded for at least 23 hours. The location of the LES was determined by high-resolution manometry (HRM). Participants were asked to discontinue PPIs for at least 2 weeks, and they were also asked not to take H₂-antagonist, prokinetic agents, and antacid for at least 3 days prior to MII-PH study. They were also asked to avoid eating fruit juice and acidic beverages during the examination. When esophageal pH remained below 4 in the distal esophagus, a total esophageal acid exposure of time (EAET) of >4.0% was used to define elevated acid exposure. HRM was

performed using 23-channel silicone-customized water-perfused catheter (manufactured by Mui Scientific, Ontario, CA). Before each procedure, transducers were calibrated to 0 and 100 mmHg using externally applied pressure. These studies were conducted with the participants in the supine position after at least a 6-hour fast. The catheter used was a water-perfused catheter, with an outside diameter of 3.8 mm (manufactured by Mui Scientific, Ontario, CA). The catheters had 1 distal channel for gastric recording, 5 channels 1 cm apart for the LES pressure, and 16 proximal channels, each 2 cm apart. Microlumina was perfused with a pneumohydraulic perfusion system (MMS software) at a water perfusion rate of 0.15 mL/min. Pressure data were acquired and presented using a software specially designed for high-resolution manometry (MMS v 8.23). The HRM assembly was passed transnasally. LES was detected using the stationary pull-through method. Then, 10 swallows of 5 mL ambient temperature water spaced more than 20 seconds apart were recorded. The pressure topography metrics were utilized in the Chicago Classification Version 3. Based on this consensus, integrated relaxation pressure 4 (IRP4) defined the lowest mean of abnormal esophagogastric junction pressure for 4 contiguous or non-contiguous seconds of relaxation. The distal contractile integral (DCI) is calculated by amplitude \times duration \times length (mmHg-s-cm) of the distal esophageal contraction greater than 20 mmHg from the proximal to distal pressure troughs. The distal latency (DL) is measured from the upper esophageal sphincter relaxation to the CDP. The contractile deceleration point (CDP) represents the inflexion point in the contractile front propagation (7). Ineffective esophageal motility (IEM) is diagnosed when $>50\%$ of the swallows are ineffective, either failed (DCI <100 mmHg cm s) or weak (DCI 100–450 mmHg cm s) peristalsis. Fragmented peristalsis is defined as $>50\%$ of the swallows with a large break (>5 cm) and not matching criteria for ineffective esophageal motility (Kahrilas et al., 2015; Chen & Hsu, 2013).

Data Analysis:

Analysis of the impedance signals included the total number of reflux episodes as regards to pH and its composition. Liquid reflux was defined as a sequential decrease in impedance to a minimum of 50% of the baseline value. Gas reflux was defined as a rapid (3kOhm/s) increase in impedance. Mixed reflux was defined as gas reflux that occurred during or immediately preceding liquid reflux. Acid reflux is defined as a reflux event associated with a drop in esophageal pH <4 ; weakly acid is associated with a pH drop between 4 and 7; and nonacid is a reflux event associated with a pH drop <7 . Meal times were excluded from the analysis.

Statistical Analysis:

Data were entered into SPSS Version 20 after encoding for each participant. Age was reported as mean \pm standard deviation. Statistical significance was compared between the symptom categories using either the Mantel-Haenszel chi square test with Yates' correction, or Fisher's exact probability test. A *p*-value less than 0.05 was considered statistically significant.

3. Results

This case-control study was conducted on 1134 participants out of 1148 participants with nonerosive gastroesophageal reflux disease (NERD) who were selected based on the results of a GERD questionnaire and esophagogastroduodenoscopy (EGD). However, 14 patients with fragmented peristalsis were excluded from the study and even their data have not been included in the tables. The case group included 325 NERD participants, of whom 152 (46.7%) were female, with an average age of 44.7 ± 9.9 years (21-70 years). The control group consisted of 809 NERD participants with normal peristalsis, of whom 408 (50.4%) were female, with an average age of $41. \pm 8.9$ (18-69) years. The frequency of IEM and normal peristalsis in participants with NERD was 28.3% (325/1148) and 70.6% (809/1148), respectively. The frequency of fragmented peristalsis in patients with NERD was low, 1.1% (14/1148); and of these patients, 10 (71.4%) were female, with an average age of 40.3 ± 7.8 years (28-95 years); however, their data have not been included in the

tables. Mean distal contractile integral (DCI) value and mean integrated relaxation pressure4(IRP4) were significantly lower in IEM group than in normal peristalsis group, but distal latency (DL) values were comparable between the 2 groups. DeMeester scores were above the normal range in 48.9%(159/325) of the participants with IEM. Mean DeMeester score value was significantly higher in IEM group. Body mass index (BMI) and the rate of smoking were the same in the 2 groups (Table1). Of the 325 patients in IEM(Case) group, 66.7% (30/325) showed a pathological EAET (mean: 14.6%, range: 3.3%-18.6%), whereas of the 809 patients in the normal peristalsis (control) group, 43.6% (81/809) showed a pathological EAET(mean:11.8%, range: 4.7%-19.2%), and the differences were significant between the 2 groups (p = 0.02).The frequency of upright and supine position of acid reflux in IEM participants was 51.1%(23/325) in both positions, whereas the frequency of upright and supine position of acid reflux in patients with normal peristalsis was 24.8% (29/809) and 23.1%(27/809), respectively. Thus, the differences between the 2 groups were significant (p = 0.03). The frequency of upright and supine position of weakly acid reflux in IEM patients was 48.9%(22/325) and 20.0(9/325), respectively. The prevalence of upright and supine position of weakly acid reflux in participants with normal peristalsis was 25.6%(30/809) and 29.9(35/809), respectively. Thus, the differences between the 2 groups was significant in upright position (p = 0.03). Also, mixed reflux was less frequent in patients with IEM than those with normal peristalsis in supine position [35.5%(16/325) vs. 48.7%(57/809)]. However, the difference was not significant between the 2 groups (p>0.4). Also, gas reflux was less frequent in patients with IEM than in those with normal peristalsis in supine position [15.5%(7/325) vs. 40.2% (47/809), p = 0.03]. The prevalence of liquid reflux in supine position was more frequent in IEM group than in normal peristalsis group [20.0%(9/325) vs. 8.5% (10/809), P = 0.03]. The prevalence of non-acid reflux in both positions was lower in IEM group compared to normal peristalsis group (Table2).

Table 1. Demographic Information and Prevalence of Manometry Findings and DeMeester Score in 1134 Patients with Nonerosive Reflux Disease (NERD)

Findings	NP (n=809)	IEM (n=325)	P-Value
Sex			
Female (%)	408(50.4)	152(46.7)	NS
Male (%)	401((49.6)	173(53.3)	
Age			
Mean±SD, year	41.6±8.9	44.7±9.9	-
Range, year	18-69	21-70	
BMI(Kg/m2) (Range)	20.6(17.8-44.9)	21.4(18.8-45.9)	NS
Smoking	94(11.6)	30(9.2)	NS
Manometry criteria			
IRP4 (mmHg, Mean±SD)	6.2±1.2	3.0±1.5	S
DCI (mmg.s.cm, Mean±SD)	1402.5±109.8	407.9±78.6	S
DL (s, Mean±SD)	6.7±0.8	6.6±0.7	NS
DeMeester score (Mean±SD)	19.7±9.3	48.1±10.8	S

NP: Normal peristalsis; IEM: Ineffective esophageal motility; SD: Standard deviation; BMI: Body mass index; IRP4: Integrated relaxation pressure 4; DCI: Distal contractile integration; DL: Distal latency; NS: Not significant; S: Significant

Table 2. Prevalence of the EAET and Reflux Episodes as Regards to pH and Its Compositions Based on Body Position of 1134 Patients with Nonerosive Reflux Disease (NERD)

Findings	NP n(%)	IEM n(%)	P-Value
EAET	51(43.6)	30(66.7)	S
Acid reflux episodes			
Upright	29(24.8)	23(51.1)	S
Supine	27((23.1)	23(51.1)	S

Weakly acid reflux	30(25.6)	22(48.9)	S
Upright	35(29.9)	9(20.0)	NS
Supine			
Non- acid reflux episodes			
Upright	5(4.27)	0	-
Supine	3(2.56)	0	-
Liquid reflux episodes			
Upright	4(3.4)	1(2.2)	NS
Supine	10(8.5)	9(20.0)	S
Mixed reflux episodes			
Upright	65(55.6)	30(66.7)	NS
Supine	57(48.7)	16(35.5)	NS
Gas reflux episodes			
Upright	64(54.7)	29(64.4)	NS
Supine	47(40.2)	7(15.5)	S

NP: Normal peristalsis; IEM: Ineffective esophageal motility; EAET: Esophagea acid reflux time; n: Number; NS, Not significant; S: Significant

4. Discussion

To the best of our knowledge, this was the first Iranian study to date to examine the prevalence of esophageal multichannel intraluminal impedance-pH (MII-PH) monitoring findings in patients with minor disorders of peristalsis of esophageal peristalsis, presented by non-erosive reflux disease (NERD). The results of this study revealed that total esophageal acid exposure of time (EAET), acid, and weakly acid reflux were more prevalent in NERD participants with ineffective esophageal motility (IEM) than in patients with normal peristalsis. DeMeester score was positive in 48.9% of the participants with IEM. Integrated relaxation pressure₄ (IRP₄) and mean distal contractile integral (DCI) were lower in patients with IEM than in patients with normal peristalsis. Body mass index (BMI) and the rate of smoking were the same in the 2 groups. Recent findings revealed that esophageal bolus transit abnormalities and presence of IEM have been strongly implicated in gastroesophageal reflux disease (GERD) development. Effective (chemical and volume) clearance depends on swallow-induced peristaltic waves (Frazzoni et al., 2013). The noxious gastric juice into the esophagus is the main cause of esophageal injuries and symptoms. Also, an increase in the duration of exposure of gastric juice, which occurs in patients with IEM, causes esophageal mucosal injuries and symptoms in GERD patients (Tack & Pandolfino, 2018). Effective esophageal peristalsis helps clear esophagus from refluxate and reduce exposure to noxious components of gastric juice. Little is known about the correlation between esophageal dysmotility and reflux episodes as regards to pH (acid, weakly acid, and nonacid) and composition (liquid, gas, and mixed reflux episodes) in participants with NERD. However, Wu et al. reported that esophageal motility disorder is less common in NERD patients than in those with erosive esophagitis (Chen & Hsu, 2013). Kahrilas et al. found that peristaltic dysfunction (defined as failed or hypotensive primary peristalsis) occurs in 25% to 48% of oesophagitis cases. Also, Diener et al. reported that severe ineffective esophageal motility disorder is associated with more severe GERD presentation (Savarino et al., 2013). In recent studies, the latest version (Version 3) of the Chicago Classification was directly compared to the previous version and it was found that minor disorders of peristalsis of esophagus are diagnosed significantly less often by the latest version and that these patterns are more often classified as normal events in symptomatic patients (Rohof & Bredenoord, 2017). One of the main clinical applications of HRM is to assess the integrity of peristalsis. Roman et al. indicated that large and small breaks (more than 5 cm and 2-5cm) in 20-mmHg isobaric contour and failed peristalsis are frequently associated with bolus escape and incomplete bolus clearance (Roman et al., 2011). Based on the Chicago Classification Version 3, the first step to detect esophageal motility disorders of esophagus is to evaluate the relaxation of the esophagogastric junction by the IRP₄. However, if the IRP₄ would not increase in the patients,

meaning that it remains at less than 15mmHg.cms, then, peristalsis is classified as major or minor motor disorders of peristalsis of esophagus based on absence, distal latency, DCI, and fragmentation. Minor disorders of peristalsis of esophagus are observed in healthy controls in contrast to major disorders of esophageal contraction. Esophageal motility is normal when a patient has a normal IRP4 and more than 50% of swallows are effective. Minor disorders of peristalsis of esophagus are classified as ineffective esophageal motility (IEM) and fragmented peristalsis (FP) (Rohof & Bredenoord, 2017; Savarino et al., 2013; Kahrilas et al., 2015). Ravi et al. reported that minor disorders of peristalsis of esophagus were poorly associated with symptoms or esophageal stasis; they also found that the vast majority of participants never developed severe symptoms in the 6.4 years and that more than 70% of the patients even became completely asymptomatic (Ravi et al., 2015). NERD is defined as a subcategory of GERD patients characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions or breaks at conventional endoscopy. The present study had some limitations. First, some patients on long- term PPI therapy who had referred to the Motility Disorders Laboratory of Firoozgar hospital previously, met our exclusion criteria. Second, participants who had fragmented peristalsis were excluded from study. Third, not all our participants had accepted MII-pH-monitoring, so it could have had a different prevalence. Fourth, nonacid reflux had overlap symptoms with bile reflux that could not be identified with MII- pH technique. Thus, further studies are needed to confirm the association between minor disorders peristalsis of esophageal and nonerosive esophagitis by assessing bolus clearance time (BCT) and post- reflux swallow-induced peristaltic wave (PSPW) index.

5. Conclusion

The present study revealed that acid, weakly acid, and gas reflux were more prevalent in nonerosive reflux disease (NERD) participants with ineffective esophageal motility disorder than in patients with normal peristalsis. The mean DeMeester score was above the normal value in both groups. Mean integrated relaxation pressure4(IRP4) and distal contractile integral (DCI) were significantly lower in those with ineffective esophageal motility disorder than in those with normal peristalsis. Thus, esophageal manometry and esophageal multichannel intraluminal impedance-pH (MII-PH) monitoring are essential for refractory NERD patients with minor disorders of peristalsis of esophagus or for those with ineffective esophageal motility disorder, shown in high- resolution manometry (HRM).

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