Reflux Patterns Characteristics of Iranian Patients with Nonerosive Reflux Disease (NERD) Based on 24-Hour Multichannel Intraluminal Impedance-pH (MII-PH) Monitoring Tests

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Abstract

Introduction: Nonerosive gastroesophageal reflux disease (NERD) is the most common gastroesophageal reflux disease (GERD) and is associated with acid, weakly acid, nonacid, liquid, and mixed reflux. The present study aimed at evaluating the differences among gastroesophageal reflux patterns, number of reflux episodes and its composition in patients with NERD using combined multichannel intraluminal impedance-pH (MII-pH) monitoring tool in the Iranian population.

Materials and Methods: This study was conducted on 670 participants aged 11 to 65 years, with nonerosive gastroesophageal reflux disease (NERD). They were selected using a questionnaire and esophagogastroduodenoscopy findings. Esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring test was performed for all the patients. The number of reflux episodes and their composition, DeMeester score, symptom index (SI), and symptom associated probability (SAP) were recorded.

Results: Of 670 patients who had NERD, 49.5% (332/670), 65.1% (436/670), and 4.0% (27/670) had acid, weakly acid, and nonacid reflux, respectively. Moreover, 11.8% (79/670), 89.2% (598/670), and 77.5% (519/670) had liquid, mixed, and gas reflux, respectively. DeMeester scores were above the normal range in 39.4% (264/670) of the patients. The symptom index (SI) and symptom-association probability (SAP) score, regardless of PH, were 34.6% (232/670) and 58.4% (391/670) above the normal range, respectively.

Conclusion: The present study revealed that weakly acid reflux was more prevalent in patients with nonerosive reflux disease (NERD) than in those with acid or nonacid reflux. Also, gas (and mixed) reflux was more frequent than liquid reflux. No significant difference was found between upright and supine position of acid, weakly acid, and nonacid reflux in patients with NERD (P>0.05).The diagnostic value of the DeMeester score, symptom index (SI), and symptom associated probability (SAP) was less than 50%.

Key words: GERD, Heartburn, NERD, MII-pH, EE

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Introduction

Gastroesophageal reflux disease (GERD) is currently defined as a condition that develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms or complications. The prevalence of GERD based on symptoms has been reported to be 20% and is increasing in both Western and Asian populations [1]. Recent studies documented that most patients with GERD have typical symptoms such as heartburn or regurgitation in the absence of endoscopic esophagitis, which is called nonerosive esophagitis (NERD) [2]. Impedance is a new tool that can measure the electrical impedance (bolus transit) among the closely arranged electrodes assembled on an intraluminal probe. Reflux is defined as either pure liquid or a mixture of liquid and gas detected by impedance. One can determine whether a reflux episode is acid, weakly acid, or nonacid when it is combined with pH monitoring. However, the bile or pepsin in refluxate cannot be determined by this method. Acid reflux episodes are defined as a pH fall <4. An overall score, known as DeMeester score, is calculated using a special formula; this value should not exceed 14.7 in healthy individuals [2].The relationship between symptoms and reflux episodes is usually expressed in NERD patients using the symptom index (SI) or symptom association probability (SAP). Conchillo et al found that acid and liquid reflux had a lower incidence in patients with NERD than in those with erosive esophagitis (EE). However, the incidence of nonacid reflux was equal in patients with NERD and EE [3]. It has been found that 30% to 40% of weakly acidic reflux events correlate with GERD symptoms [1]. The present study aimed at prospectively evaluating the differences in the total number of reflux episodes and its composition in patients with nonerosive esophagitis (NERD) based on the new technique of combined multichannel intraluminal impedance-pH(MII-PH) monitoring in the Iranian population.

Methodology

1. Patients

This study was conducted on 950 patients (11-84 years) with gastroesophageal reflux disease (GERD) during August 2012 and July 2017. GERD was defined as having any degree of reflux esophagitis on endoscopy, heartburn, regurgitation, or noncardiac chest pain (NCCP) on a weekly basis during the last 3 months. The participants were selected from those who referred to our endoscopy ward. All the patients provided informed consent and accepted to complete a standard questionnaire on heartburn, regurgitation, and NCCP. Esophagogastroduodenoscopy (EGD) was done for all the patients in the same center by expert endoscopists. Reflux esophagitis was diagnosed and graded using Los Angeles classification. Of the total participants, 70.5% (670/950) aged 11 to 65 years had GERD symptoms without esophagitis (nonerosive reflux disease (NERD). Esophageal manometry and esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring were performed for all patients. The exclusion criteria were as follow: previous foregut surgery, cardiovascular diseases, history of malignant diseases, pregnancy, breastfeeding, psychiatric illness, history of alcohol or drug abuse, large hiatal hernia, and esophageal varices. GERD symptoms (heartburn, regurgitation, and NCCP), and negative esophagitis in EGD were included. Achalasia findings in barium swallow, esophageal manometry, or EGD were excluded. All patients accepted to undergo esophageal manometry before MII-pH.

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

Esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring was performed on an outpatient basis 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, allowing the simultaneous pH analysis in the distal esophagus. MII-PH data were recorded for at least 23 hours and properly downloaded. The location of the lower esophageal sphincter (LES) was determined by high resolution manometry (HRM) using 23-channel silicone-customized water-perfused catheter (manufactured by Mui Scientific, Ontario,CA). The proton pump inhibitors (PPIs) were evaluated and the patients were asked to discontinue PPIs for at least 2 weeks, and H2-antagonist, prokinitic agents and antacid for at least 3 days prior to MII-PH study. The patients were advised to continue daily regular activities and have a minimum of 3 standard meals during the study period. In addition, the patients were asked to avoid eating fruit juice and acidic beverages including apple, orange, or lemon juice during the examination and to push the symptom indicator button on the MII-pH each time they experienced heartburn or regurgitation and chest pain. The following parameters were obtained from MII-PH recordings. The esophageal acid exposure of time (EAET) provided a quantitative measure of the time when esophageal pH remained below 4 in the distal esophagus, expressed as a percentage. A total EAET of >4.0% was used to define elevated acid exposure, then, upright and recumbent were separately calculated. This test had a sensitivity of 91% and specificity of 85% for discriminating acid reflux [4, 5].

3. Data Analysis

Impedance and pH tracings were analyzed by the researcher. Analysis of the impedance signals included the total number of reflux episodes as regards to composition (liquid, gas, and mixed reflux episodes) and pH (acid, weakly acid, and nonacid). Liquid reflux was defined as a sequential decrease in impedance to a minimum of 50% of the baseline value, beginning at the most distal recording site. Gas reflux was defined as a rapid (3 kOhm/s) increase in impedance, occurring simultaneously in at least 2 esophageal measuring segments in the absence of swallowing. Mixed liquid-gas reflux was defined as gas reflux that occurred during or immediately preceding liquid reflux. For each reflux, episodes detected by impedance

at 5 cm above the LES were calculated as the time(s) between the 50% drop in impedance until the 50% recovery of the impedance baseline. 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.

The meal periods were excluded from the analysis. DeMeester score was calculated based on 6 variables (percentage of the total time that pH was <4; percentage of upright and supine time that the pH was <4; number of reflux events; number of reflux events longer than 5 minutes; and longest reflux event). Acid reflux episodes are defined as a pH fall <4. An overall score, known as DeMeester score, is calculated using a special formula; this value should not exceed 14.7 in healthy individuals [2]. The symptom index (SI) and symptom association probability (SAP) were calculated according to the formula described previously. SI was defined as the number of symptoms associated with reflux divided by the total number of symptoms; at least 1 symptom is required for SI to be positive. SAP was calculated by dividing 24- hour pH data to 2-minute segments; the probability of symptom distribution and reflux episodes in a 2 minute-window was then calculated to determine if it could have occurred by chance (Fisher test); SAP = 1-p.SI and SAP were considered to be positive at ≥ 50% and ≥ 95%, respectively. The normal values of the MMS MII-PH system were reported by Zerbib et al. [6].

Statistical Analysis

Data were entered into SPSS Version 19 after encoding for each participant. Age was reported as mean ± standard deviation. Comparison of statistical significance was made between the symptom categories using either the Mantel-Haenszel chi-square test with Yates correction, or the Fisher's exact probability test. A p value less than 0.05 was considered statistically significant.

Results

This study was conducted on 670 patients, who met our inclusion criteria and had GERD symptoms (heartburn and/or regurgitation and noncardiac chest pain) without esophagitis. The mean age of the patients was 40.4±9.6 years (range: 11-63 years), and of them, 62.4% (418/670) were female. The mean age of the female and male patients was 39.5±9.3 years (age range: 11-63 years) and 41.2±8.4 years (age range: 12-63), respectively. Based on the total number of reflux episodes, of the patients, 49.5% (332/670), 65.1% (436/670), and 4.0% (27/670) had acid, weakly acid, and nonacid reflux, respectively. Also, 11.8% (79/670), 89.2% (598/670), and 77.5% (519/670) of the patients had liquid, mixed, and gas reflux, respectively. DeMeester scores were above the normal range in 39.4% of the participants (264/670). The symptom index (SI) and symptom association probability (SAP) score, regardless of PH contents (acid, weakly acid, or nonacid) were above the normal range in 34.6% (232/670) and 58.4% (391/670), respectively (Table 1). The acid, weakly acid, liquid, mixed, and gas reflux were more frequent in males than in females, but gas reflux was more frequent in the upright position than in the supine position and weakly acid and mixed reflux were more frequent in the supine position than in the upright position. There were not any significant differences between upright and supine position in acid, weakly acid, nonacid, liquid, and mixed reflux in patients with NERD (P>0.05). Nonacid and liquid refluxes were not prevalent, but gas reflux occurred more frequently in patients in this study. SI was 23.6% (158/670), 2.4% (16/670), and 0% (0) above the normal value in acid, weakly acid, and nonacid reflux, respectively. SAP was 48.8% (327/670), 32.7% (226/670), and 7.2% (48/670) above the normal value in acid, weakly acid, and nonacid reflux, respectively (Table 2).

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 nonerosive reflux disease (NERD) associated with diverse types of reflux patterns. The results of this study revealed that weakly acid was more prevalent than acid in patients with NERD. DeMeester score number was positive in less than 50% of the total patients.

The symptom association probability (SAP) score was 48.8% positive in acid reflux and more frequent than weakly acid and nonacid reflux. The acid, weakly acid, liquid, mixed, and gas reflux were more prevalent in males than in females, however, nonacid reflux was more prevalent in females. Although acid, nonacid, and gas reflux were more frequent in the upright position than in the supine position and weakly acid and mixed reflux were more frequent in the supine position, no significant differences were found between upright and supine positions in acid, weakly acid, nonacid, liquid, and mixed reflux in patients with NERD (P>0.05). Nonacid and liquid refluxes were not prevalent in this study, but gas reflux was more prevalent. It seems that SI and SAP are more closely correlated with symptoms in acid reflux than in nonacid reflux.

Although Gastroesophageal Reflux Disease (GERD) Questionnaire and Proton pump inhibitor s(PPIs) test could diagnose patients with GERD, the definitive diagnosis of GERD still depends on endoscopy or MII-pH monitoring. Savarino et al. have proposed subtypes of NERD patients based on cooperation between MII-pH findings and symptom association probability (SAP) results as pH-positive and negative NERD (including hypersensitivity esophagus and functional heartburn)(7). On the other hand, if the parameters of reflux such as total number of reflux episodes based on acid, nonacid, or mixed reflux were above the normal limits and SI or SAP parameter were positive, then, the patient would be considered to have a reflux related disease. However, if the parameters of reflux such as total number of reflux episodes were within the normal limits but SI or SAP indexes were negative, then, the patient would be considered to have a non-reflux related disease. NERD is the most common presentation of GERD and comprises up to 69% of all Iranian patients with GERD [8], which suggests that the chemical stimuli (acid, weakly acidic, bile and proteolytic

Table 1: Demographic Information and reflux characteristics of 670 Patients With non-erosive reflux disease (NERD) and correlation between onset of reflux episodes to the symptoms index

Findings	NERD, n (%)
Numbers	670(100)
Age(years)	
Mean ±SD	40.4±9.6
Range	12-63
Sex	
Female, n (%)	418(62.4)
Male, n (%)	252(37.6)
Reflux episodes (Total)	
Acid, n (%)	332(49.5)
Weakly acid, n (%)	436(65.1)
Non acid, n (%)	27(4)
Reflux composition (Total)	
Liquid, n (%)	79(11.8)
Mixed, n (%)	598(89.2)
Gas, n (%)	519(77.5)
De Meester Score, n (%)	264(39.4)
SI Total, n (%)	232(34.6)
SAP Total, n (%)	391(58.4)

Table 2: Demographic Information and prevalence of reflux episodes of 670 Patients With non-erosive reflux disease(NERD), reflux episodes based on body position and correlation between onset of reflux episodes to the symptoms index

Findings	Patients with NERD ,n=670					
	Acid reflux +	Weakly Acid reflux+	Non Acid reflux+	Liquid reflux+	Mixed reflux+	Gas reflux+
Patients, n (%)	332(79.5)	436(65.1)	27(4.0)	79(11.8)	598(89.2)	519(77.5)
Gender						
Female, n (%)	110(33.1)	204(46.8)	21(77.8)	35(44.3)	253(42.3)	234(45.1)
Male, n (%)	222(66.9)	232(53.2)	6(22.2)	44(55.7)	345(57.5)	285(54.9)
Body position:						
Upright, n (%)*	177(26.4)	208(31.0)	16(2.4)	21(3.1)	286(42.7)	519(77.5)
Supine, n (%)	155(23.1)	228(34.0)	11(1.6)	58(8.6)	312(46.6)	265(39.5)
Symptom Index:						
SI, n (%) **	158(23.6)	16(2.4)	0(0)	-	-	-
SAP, n (%) ***	327(48.8)	226(32.7)	48(7.2)	-	-	-

enzymes), mechanical stimuli (distension or contraction), peripheral, and central hypersensitivity are the main causes of NERD (or GERD). The esophageal sensitivity, large volume, and proximal extent of refluxate are other putative mechanisms of patients with NERD. The pathogenesis of NERD for each patient is based on the results of MII-pH monitoring. The multiple intraluminal impedance pH (MII-PH) monitoring has been introduced as a new and reproducible technique to diagnose and assess the outcome of anti-acid secretory drugs. This tool could detect reflux episodes independent of the pH of the refluxate, so it identifies who has nonacid reflux. Combined pH and intraluminal impedance monitoring could identify all types of reflux events with respect to acidity (acid, weakly acidic, weakly alkaline) and its composition (liquid, gas, and mixed), and it is more accurate than pH alone in detecting both acid and weakly acidic reflux. The direct positive relationship between the esophageal acid exposure time (EAET) and the degree of mucosal damage have been shown by several studies [4]. Bredenoord et al. recommended that MII-PH monitoring esophageal manometry be done based on PPI because it can show the correlation between native oesophageal acid exposure and degree of mucosal damage [4]. In this study, total acid reflux episode was (49.5%) lower than the previous report. Conchillo et al. found that acid and liquid reflux in the supine position of the patients with NERD were lower than erosive esophagitis (EE), but patients with EE and NERD have similar nonacid reflux patterns [3]. Namasivayam et al. found that 30% to 40% of weakly acidic reflux episodes

episodes correlate with symptoms [1]. Weakly acidic reflux is uncommon in patients with GERD, who are tested for acid suppressive medication (14.8%); it mainly occurs in patients treated with PPI and in the postprandial period. However, in this study, weakly acid was more frequent than acid and nonacid reflux; they were tested based on PPI. It is suggested that preceded acid reflux before weakly acid reflux is the pathogenesis of esophageal symptom in NERD patients [1]. NERD patients with pH-negative are more sensitive to weakly acidic reflux than patients with erosive esophageal reflux disease (ERD) [9]. Moreover, experiments have revealed that exposure of nonacid materials and bilirubin to esophagus can provoke esophageal injuries and heartburn, but it is a mechanism in patients with NERD, which is not fully elucidated [6]. Although nonacid reflux was not prevalent in this study, several studies have supported the role of nonacid reflux as a cause of symptoms in NERD patients, especially those not responding to proton pump inhibitors (PPIs) [6]. Gas (and mixed) reflux was more frequent than liquid reflux in this study, suggesting that the presence of gas in the refluxate of patients with NERD significantly enhances the probability of reflux perception. These patients are also more sensitive to less acidic reflux than patients with oesophagitis. Temporal relationship between symptoms and reflux episodes is a method used in evaluating the results of combined pH-impedance monitoring in NERD patients. This method is only recommended for NERD patients with hypersensitivity esophagus and functional heartburn, those whose EAET results was negative in MII-pH test [10]. In this study, the frequency of the patients with positive SAP (48.8%) was more than patients with positive SI (23.6%) in acid reflux pattern. The present study had some limitations. First and foremost was that nonacid reflux had overlap symptoms with bile reflux that could not be identified with MII- pH technique. Second, not all our patients had accepted MII-pH-monitoring, so it could have had a different prevalence. Third, some patients on long-term PPI therapy who referred to the Motility Disorders Laboratory of Firoozgar Hospital before, met our exclusion criteria.

Conclusions: The present study revealed that weakly acid reflux was more prevalent in patients with nonerosive reflux disease (NERD) than those with acid or nonacid reflux. Also, gas (and mixed) reflux was more frequent than liquid reflux. There were no significant differences between upright and supine position of acid, weakly acid, and nonacid reflux patients with NERD (P>0.05). The diagnostic value of the DeMeester score, symptom index (SI), and symptom associated probability (SAP) was less than 50%. Further studies should be conducted to determine the effectiveness of other stimulates as bilirubin and pepsin on esophageal symptoms and histological injuries.

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