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# Functional heartburn in Iranian patients with non-erosive gastroesophageal reflux disease



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## ABSTRACT

**Aim:** Esophageal multi channel intraluminal impedance-PH (MII-PH) monitoring is a new technique used for detecting the flow of fluids and gas through the esophagus, using the differences in electrical impedance between the mucosal surface, fluids, and gas that surround the catheter. The aim of this study was to determine the frequency of functional heartburn in Iranian patients with non-erosive gastroesophageal reflux disease (NERD).

**Methods:** In this study, 940 patients aged 11-84 years, with the chief complaint of heartburn were selected. The MII-PH monitoring was done in 215 of the patients who did not have esophageal injuries (NERD).

**Results:** Of the participants who filled the questionnaire, 29.4% experienced heartburn at least once a week, 24.1% had it twice daily,

and 21.3% had it after each meal. The mean age of the patients with heartburn was  $36.97 \pm 10.8$  (Range: 21- 57) years. Of the patients, 51.2% were female. MII-PH monitoring was done in 215 participants, with non-erosive esophagitis. Esophageal acid exposure of time (EAET) was negative in 42.8% and positive in 57.2% of the NERD patients. Of the patients, 39.1% and 18.1% had functional heartburn (FH) and hypersensitive esophagus (HE), respectively

**Conclusion:** Functional heartburn and non-erosive gastroesophageal reflux disease are prevalent in the Iranian population. Esophageal multi channel intraluminal impedance-PH (MII-PH) monitoring is essential for discriminating functional heartburn from other types of non-erosive gastroesophageal reflux diseases.

**Keywords:** GERD, NERD, FH, HE, MII-PH

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## INTRODUCTION

Heartburn is one of the most frequent upper gastrointestinal symptoms in patients with dyspepsia. The prevalence of heartburn is 8.8% -25.9% in Europe, 18.1% -27.8% in North America, but only 2.5%-7.8% in East Asia.<sup>1,2</sup> It reported that the weekly prevalence of gastroesophageal reflux disease (GERD) in the Iranian population is different, from 6 to 33%.<sup>3</sup> Heartburn and regurgitation are primary symptoms in GERD patients. Non-erosive gastroesophageal reflux disease (NERD) characterized by the presence of classic GERD symptoms in the absence of esophageal mucosal break on upper endoscopy,<sup>4</sup> and it is estimated to constitute 50% to 70% of the GERD population in the Western and European countries. In Asia, NERD has been reported to affect different ethnic GERD groups, from 60 to 90% of the population.<sup>5</sup> Based on the multi channel intraluminal impedance-PH (MII-PH) monitoring, the patients with NERD were classified into three groups: NERD with pathological reflux and without pathological reflux, the latter included functional heartburn (FH) and hypersensitive esophagus (HE). This technique allows the recognition of both acidic, weakly acidic and non- acid reflux episodes.<sup>6</sup> Impedance monitoring is a new technique for detecting the flow of fluids and gas through the esophagus, using the differences in

electrical impedance between the mucosal surface, fluids, and gas that surround the catheter. Recently, a correlation was found between heartburn and regurgitation and patients with pathological esophageal acid exposure time (EAET).<sup>5</sup> Savarino et al. studied 200 patients with NERD and reported that 40.5% of them were EAET positive, and 59.5% were EAET negative. Moreover, 32 and 27% of these patients had HE and FH, respectively.<sup>7,8</sup> The aim of this study was to determine the frequency of functional heartburn in Iranian patients with NERD.

## MATERIAL AND METHODS

### Patients

This study was conducted on 940 patients aged 11-84 years, with the chief complaint of heartburn (defined as a burning feeling in epigastric area that rises through the chest in the substernal area) of over the three-month duration, who referred to the endoscopy ward of Firoozgar hospital from September 2012-2016. All the patients provided informed consent and accepted to complete a standard questionnaire about heartburn and regurgitation. Esophagogastroduodenoscopy (EGD) was done for all the patients in the same center by expert endoscopists. Patients with heartburn and regurgitation were included. The exclusion criteria were

as follows: History of malignant diseases, previous foregut surgery, cardiovascular diseases, pregnancy, breastfeeding, psychiatric illness, history of alcohol or drug abuse, large hiatal hernia, and esophageal varices. Moreover, those with achalasia in barium swallow or EGD were excluded. The frequency of the symptoms of heartburn and regurgitation, and the answers were graded on a three-point of Likert scale as follows: Mild = symptoms that could be easily ignored, moderate = awareness of symptoms but easily tolerated and advanced severity = symptoms sufficient to interfere with normal activities. Smoking was recorded as positive or negative. Body mass index (BMI) was calculated by weight in kilogram in fasting state divided by square of height in meters.

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

MII-PH monitoring was performed on an out-patient basis, using an ambulatory, MII-pH system (manufactured by Mui Scientific, Ontario, CA). The MII-PH catheter (Unisensor AG, Bahnstr, Switzerland), with six impedance electrodes and one PH sensor (K6011-EI-0632), was inserted transnasally. Impedance measuring sites were located in the distal esophagus at 3, 5, 7 and 9 centimeters and two impedance-measuring sites in the proximal esophagus at 15 and 17 centimeters above the LES. One antimony pH sensor was located in 5 centimeters above the LES, allowing for simultaneous PH analysis in the distal esophagus. MII-PH data were recorded for at least 23 hours and correctly downloaded. The location of the lower esophageal sphincter was determined by high-resolution manometry (HRM), using a 23-channel silicone-customized water-perfused catheter (manufactured by Mui Scientific, Ontario, CA). The participants were evaluated, using proton pump inhibitors (PPIs), and were asked to discontinue PPIs for at least two weeks and avoid taking H<sub>2</sub>-receptor antagonist, prokinetic agents and antacid for at least three days before MII-PH study. The patients were advised to continue their regular daily activities and to have a minimum of three standard meals during the study period. Also, they 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. The following parameters were obtained from MII-PH recordings: The esophageal acid exposure of time (EAET) provided a quantitative measure of the time for which esophageal PH remained below 4 in the distal esophagus, expressed as a percentage. A total EAET of >4.0% was used to define a

high acid exposure; upright and recumbent were not separately calculated. This test had a sensitivity of 91% and specificity of 85% for discriminating acid reflux.<sup>9</sup> The symptom associated probability (SAP) test was calculated by dividing 24 hours pH data into 2-minute segments, the probability of symptom distribution and reflux episodes in the 2 minute-window. Then it calculated to determine if it could have occurred by chance (Fisher test); SAP = 1-p was considered positive if it was > 95% for acid reflux.<sup>7</sup> In this study, if EAET and SAP, both, were negative, it was called functional heartburn, and if EAET was negative but SAP was positive, it was then named hypersensitivity esophagus.<sup>8</sup>

### Data Analysis

Data were entered into SPSS Version 18 after encoding for each participant. Age was reported as a mean  $\pm$  standard deviation. The results were expressed as odds ratios (ORs), with 95% confidence intervals (CIs). Comparison of statistical significance was made between the symptom categories, using the Mantel-Haenszel chi-squared test either with Yates correction or with the Fisher's exact probability test. A *p* value of less than 0.05 was considered statistically significant.

## RESULTS

In this study, 3,318 patients had dyspepsia (2012-2016); of them, 123 had achalasia in barium swallow and esophageal manometry, so they were excluded. Moreover, 29.4% (940/3195) of these patients had heartburn at least once a week, 24.1% (770/3195) had it twice daily, and 21.3% (675/3195) had it after each meal. Also, 23.4% (748/3195) of the patients had regurgitation at least twice a week. The mean age of the patients with heartburn was 36.9  $\pm$  10.8 (Range: 21-57) years, and 51.2% (63/123) were female. Of the patients with heartburn, 28.1% (264/940) had erosive esophagitis, and 71.9% (676/940) had normal esophagogastroendoscopy results and had the non-erosive gastroesophageal disease (NERD). Of these patients, 215 patients, who had both symptoms (heartburn and regurgitation) were accepted, and esophageal multi channel intraluminal impedance-PH (MII-PH) monitoring was done for them. MII-PH monitoring results revealed that 42.8% (92/125) of the patients with NERD were negative for esophageal acid exposure of time (EAET) and 57.2% (123/215) were positive for EAET. Of the former group, 39.1% (84/125) and 18.1% (39/215) had functional heartburn (FH) and hypersensitive esophagus (HE), respectively. The mean age of the patients with FH was 38.9  $\pm$  11.2 (Range: 21-57) years, and the

**Table 1** The Demographic Information of Patients with Functional Heartburn and Hypersensitive Esophagus in 215 Patients with NERD

Findings	Total EAET Negative N (%)	Functional Heartburn n (%)	Hypersensitive Esophagus n (%)	Odds Ratio (95% CI)	P-Value
Number of patients	123(57.2)	84(39.1%)	39(18.1)		
Age (years)					
Mean $\pm$ SD, years	36.9 $\pm$ 10.8	38.9 $\pm$ 11.2	35.4 $\pm$ 10.3	0.9(0.2-2)	0.27
Range, years	21-57	21-57	23-57		
Female, n (%)	63(51.2)	45(53.6)	18(46.1)	1.3(0.8-2.8)	0.39
Smoking	14(11.4)	10(11.9)	4(10.2)	0.6(0.36-1.43)	0.24
BMI (Kg/m <sup>2</sup> ), (Range)	23.5(18.5-46.5)	23.9(18.5-46.6)	22.6(18.6-45.5)	0.8(0.8-2.0)	0.25
Heartburn severity					
Mild	0(0%)	0(0%)	0(0%)	-	-
Moderate	98(79.7%)	69(82.1%)	29(74.3%)	1.6(1.0-3.5)	0.36
Sever	25(20.3%)	15(17.9%)	10(25.7%)	0.6(0.2-1.4)	0.27
Regurgitation severity					
Mild	14(11.4%)	6(7.1%)	8(20.5%)	0.3(0.1-0.8)	0.29
Moderate	89(72.3%)	67(79.8%)	22(56.4%)	3(1.3-6.5)	0.02
Sever	20(16.3%)	11(13.1%)	9(23.1%)	0.5(0.4-1.2)	0.31

BMI: Body Mass Index; EAET: Esophageal Acid Exposure Time; SD: Standard Deviation

mean age of the patients with HE was 35.4  $\pm$  10.3 (Range: 23-57) years. The rate of smoking was the same in patients with FH and HE. Body mass index (BMI) of the two groups was the same. However, the severity of heartburn and regurgitation was not significantly different between the two groups, except for moderate regurgitation, which was more prevalent in those with FH than in those with HE.

## DISCUSSIONS

To the best of our knowledge, this was the first Iranian esophageal PH monitoring study conducted based on esophageal MII-PH monitoring to examine the frequency of functional heartburn (FH) and hypersensitivity esophagus (HE) and determine the relationship between both and some risk factors. Our results revealed that the non-erosive gastroesophageal reflux disease (NERD) and FH were more prevalent in the Iranian population. The prevalence of NERD and FH were 71.9% and 39.1%, respectively (Table 1). Concerning the demographics of NERD patients, we did not detect any significant differences in the ratios of gender, age, and BMI between the two groups (FH and HE) as well as the ratios of smokers. Patients with NERD tended to have a lower mean percentage of esophageal acid exposure of time (EAET).<sup>6</sup> Heartburn was the most typical symptom of gastroesophageal reflux disease (GERD), and it was a common complaint of the general population. Most patients with heartburn are treated in primary care and are

not extensively examined. Heartburn of presumed esophageal origin is a disabling but common condition in Iranian patients as in the Western countries.<sup>10</sup> El-Serag et al. reported a monthly prevalence of heartburn to be 34.2-40.6% in the United States. The prevalence of GERD varies in Asia, but it is lower than the Western countries.<sup>2</sup> Heartburn results in frequent visits to emergency rooms or physician's offices. Confirmation of FH diagnosis is necessary for patients who fail to receive a standard dose of PPIs. In other words, the role of antireflux surgery in functional heartburn has not yet been studied. Heartburn and regurgitation could be originated from GERD due to mechanically impaired pathological esophageal clearance although not all patients with heartburn respond well to acid inhibitors. Most of the patients with NERD and those with normal acid exposure time were found to have "functional heartburn" (FH) in MII examination.<sup>6</sup> Before MII-PH monitoring era, diagnosis of FH was made based on the Rome II criteria, which defined functional heartburn as at least 12 in consecutive weeks of burning, retrosternal discomfort or pain, and an absence of pathologic gastroesophageal reflux, achalasia, or other motility disorders with recognized pathologic basis in 12 months.<sup>6</sup>

This diagnostic model had several dilemmas: Firstly, FH diagnosis was made based on subjective symptoms. Secondly, this method could not determine the etiology of heartburn. Thirdly, the physician could not discriminate FH from HE or other forms of NERD. Several mechanisms have been

proposed for the pathogenesis of heartburn, which includes prolonged contraction of the esophagus, visceral hypersensitivity, and psychological factors or panic disorders. The mechanism for increased esophageal chemoreceptor hypersensitivity is not known, but it may be due to penetration of acid into the deep layer of esophageal where neverending is located.<sup>4</sup> Acid-induced esophageal pain is likely to be mediated by vanilloid receptor 1 (VR1) and anion-sensing ion channels (ASICs). Moreover, recently it has been found that adenosine, an endogenous nucleotide, could induce somatic and visceral pain.<sup>11</sup>

Nonetheless, this study had some limitations, first and foremost among which was that heartburn had overlap symptoms with noncardiac chest pain (NCCP), despite all the cardiovascular workup. Secondly, the endoscopic findings were reported by two or three endoscopists in this study so that inter-observer conflicts could have occurred. Thirdly, not all our patients had accepted MII/PH examination, so it could have caused misclassification of the patients as having FH, or HE.

## CONCLUSIONS

Functional heartburn (FH) and non-erosive gastroesophageal reflux disease (NERD) are prevalent in Iranian population. The patients with FH should be considered separately from those with NERD because each is managed differently. In our opinion, multi channel intraesophageal impedance-PH (MII-PH) monitoring is essential for the diagnosis of FH in those patients with inadequate response to appropriate proton pump inhibitor (PPI) treatment. Moreover, further studies are necessary to develop the pain origin and effectiveness of therapeutic modalities, which would not probably be limited to acid suppression.

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## REFERENCES

1. Beer AM, Uebelhack R, Pohl U. Efficacy and tolerability of hydrogen carbonate-rich water for heartburn. *World J Gastrointest Pathophysiol.*2016; 7: 171–180.
2. El-Serag HB, Petersen NJ, Carter J, Graham DY, Richardson P, Genta RM, Rabeneck L. Gastroesophageal reflux among different racial groups in the United States. *Gastroenterology.* 2004;126:1692–1699
3. Alireza Delavari A, Moradi Gh, Birjandi F, Elahi E, Saberifiroozi M. The Prevalence of Gastroesophageal Reflux Disease (GERD) in the Islamic Republic of Iran: A Systematic Review *Middle East J Dig Dis.*2012; 4: 5–15.
4. Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease .a global evidence – based consensus. *Am J Gastroenterology* 2006;101:1900-1920
5. Chen CL, Hsu PI. Current advances in the diagnosis and treatment of nonerosive reflux disease. *Gastroenterology research and practice,* 2013.
6. Tack J, Fass R. Approaches to endoscopic-negative reflux disease: part of the GERD spectrum or a unique acid-related disorder?. *Alimentary pharmacology & therapeutics,* 2004; 19:28-34.
7. Bredenoord AJ. Impedance-pH monitoring: new standard for measuring gastro-oesophageal reflux. *Neurogastroenterology and motility.*2008; 20:434-439.
8. Savarino E, Pohl D, Zentilin P, Dulbeco P, Sammito G, Sconfienza L, Vigneri S, Camerini G, Tutuian R, Savarino V. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. *Gut.*2009;58:1185-91.
9. Patel A, Sayuk GS, Gyawali CP. Acid-Based Parameters on pH-Impedance Testing Predict Symptom Improvement With Medical Management Better Than Impedance Parameters. *Am J Gastroenterol* 2014;109:836–844.
10. Yaseri HF, Yaseri AMF, Moghaddam AB, Arabshahi SKS. Relationship between Esophageal Clinical Symptoms and Manometry Findings in Patients with Esophageal Motility Disorders:A Cross-Sectional Study. *Med J Islam Repub Iran* 2015; 29:271-272.
11. Knowles CH, Aziz Q. Visceral hypersensitivity in nonerosive reflux disease. *Gut* 2008; 57:674–83.



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