

Diagnostic Efficacy of 24-hr Esophageal pH Monitoring in Patients with Refractory Gastroesophageal Reflux Disease

Atoosa Gharib¹, Mojgan Forootan^{2*}, Marjan Sharifzadeh³, Saied Abdi⁴, Mohammad Darvishi⁵, Ahmad Eghbali⁶

¹Shahid Modarres Clinical Research and Development Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; ²Department of Gastroenterology, Gastrointestinal and Liver Diseases Research Center (RCGLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran; ³Shahid Beheshti University of Medical Sciences, Tehran, Iran; ⁴Department of Optometry, Shahid Beheshti University of Medical Sciences, Tehran, Iran; ⁵Infectious Diseases and Tropical Medicine Research Center (IDTMRC), Department of Aerospace and Subaquatic Medicine, AJA University of Medical Sciences, Tehran, Iran; ⁶Modares Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

BACKGROUND: Gastric reflux is one of the most important causes of the referral of patients to the internal clinic, which in some cases causes problems for patients due to resistance to common treatments. Therefore, timely diagnosis and treatment of this group of patients are very important.

AIM: The purpose of the present study was to determine the off-proton pump inhibitor (off-PPI) 24 h pH-impedance analyses in patients with refractory gastroesophageal reflux disease (GERD) attending to Taleghani Hospital since 2009 to 2017.

METHODS: In this observational descriptive-comparative off-PPI study, 572 patients with refractory GERD who were referred to Taleghani Hospital in Tehran from 2009 to 2017 were selected, and the results of 24 h pH Impedance analysis were then assessed.

RESULTS: The results of 24h pH-impedance indicated that 7% of cases belonged to Pure Acid Reflux followed by weakly Acid (1%), non-acid (0.3%), mixed & gas (5.2%), functional (58.4%) and oesophagal hypersensitivity (28%). Furthermore, weakly acid plus acid was also found to be 8% and Weakly Acid + Acid + Non-Acid were determined as 8.3%.

CONCLUSIONS: Our findings suggested that nearly more than half of the patients with refractory GERD would have a functional disorder in the 24h pH-impedance analysis.

Citation: Gharib A, Forootan M, Sharifzadeh M, Abdi S, Darvishi M, Eghbali A. Diagnostic Efficacy of 24-hr Esophageal pH Monitoring in Patients with Refractory Gastroesophageal Reflux Disease. Open Access Maced J Med Sci. 2018 Jul 20; 6(7):1235-1238. <https://doi.org/10.3889/oamjms.2018.268>

Keywords: Gastric reflux; PH Impedance; Acid plus acid; Diagnosis

***Correspondence:** Mojgan Forootan. Department of Gastroenterology, Gastrointestinal and Liver Diseases Research Center (RCGLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: mforootan2003@yahoo.com

Received: 19-Apr-2018; **Revised:** 27-May-2018; **Accepted:** 28-May-2018; **Online first:** 09-Jul-2018

Copyright: © 2018 Atoosa Gharib, Mojgan Forootan, Marjan Sharifzadeh, Saied Abdi, Mohammad Darvishi, Ahmad Eghbali. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Introduction

Reflux or gastroesophageal reflux disease (GERD) is one of the common gastrointestinal disorders, with many risk factors such as diabetes and hypertension [1]. This disorder is present in 16% of the general population and can be associated with common clinical symptoms, such as heartburn and chest pain [2]. However, clinical symptoms in GERD patients are not limited to gastrointestinal symptoms and can also be manifested as non-gastro-intestinal symptoms, including respiratory disorders, sleep disturbances, and atorvastinuratory symptoms [3]. The disease causes a 2.5-hour absence from the

workplace, a 23 per cent reduction in efficiency, and a 30 per cent reduction in the normal performance of the individual. In general, there is a significant reduction in the quality of life in patients suffering from GERD [4]. It also imposes huge costs on individuals and health systems [5]. Therefore, treatment for GERD patients is important for improving their quality of life. Treatment in this area is divided into two categories of therapeutic and surgical treatments, both of which not only reduce the severity of the symptoms of the patients but also significantly improve their quality of life [6] [7]. It is worth noting that, in both short and long-term, the effectiveness of surgical treatments is far more than pharmaceutical treatments, and drug therapies are particularly

effective on clinical symptoms such as dysphagia [6][8]. However, 40% of patients do not show any proper therapeutic response, and they refer to refractory GERD, which requires the adoption of other therapies [9]. The causes of GERD Refractory include Acid Reflux, Non-Acid Reflux, Esophageal Hypersensitivity, and Functional Heart Burn [10]. Moreover, only a few studies have been done in Iranian patients [11] [12] [13].

On the other hand, GERD is a long-term condition in which stomach contents enter the oesophagus and cause symptoms or complications. Complications include esophagitis, oesophageal strictures, and Barrett's oesophagus. There are some risk factors involved in the disease, including obesity, pregnancy, smoking, hiatus hernia, and taking some special medications. Drugs that affect gastric reflux are described to be as follow: antihistamines, calcium channel blockers, antidepressants and sleep medications. Diagnosis among people who do not respond in simple ways may be made in other ways, such as gastroscopy, oesophageal pH monitoring, and or impedance-pH monitoring [13] [14] [15] [16].

Therefore, the goal of this study was to evaluate the causes of refractory GERD in patients who referred to Taleghani Hospital from 2009 to 2017 as off- proton pump inhibitor (off-PPI).

Methods

This study was conducted by a descriptive cross-sectional study of off-PPI. A total of 572 patients with refractory GERD who referred to Tehran Taleghani Hospital from 2009 to 2017 were evaluated. Endoscopy results and response to medical treatment were controlled as interventional factors. In the manometer, the absence of motion disorders, such as achalasia and diffuse oesophageal spasm (DES), was confirmed.

The required data were extracted from patients' files, including the age, sex, duration of GERD symptoms, pH and Impedance parameters, and symptom association probability (SAP), as well as proximal extension and bolus clearance time (BCT). Then, the prevalence of different parameters of the 24h PH Impedance was extracted from them using file contents. Finally, data analysis was performed using SPSS software version 24. The mean and standard deviations were used to evaluate quantitative variables, where qualitative variables were presented as absolute and relative frequency. The tests used in this field included chi-square and analysis of variance. The significance level for the relationships between variables was considered 0.5.

Inclusion criteria

Failure of medical treatment with protein pumps inhibitors (PPIs) for at least one month, once or twice daily [12].

Exclusion criteria

- 1: Patients who had anti-reflux surgery, either PPI or H2-blocker.
2. Patients with atypical GERD symptoms.
3. Motion disorders, such as achalasia and diffuse oesophageal spasm.
4. Non-Iranian patients.
5. Patients with abnormal manometry.
6. Age younger than 18 or over 80 years old.
7. Systemic disease.

Results

In this study, 572 subjects were studied. Their mean age was 38.2 years (range 18-80 years), and mean duration of clinical symptoms was 5.1 years (from 1 to 16 years). Also, 48.3% were males, and 51.7% were females. DeMeester Score was abnormal in 44.2% of patients and Total Reflux Time in 45.5% of patients. The frequency of reflux and the frequency of long-term reflux was 40% and 24.1%, respectively. In 2.6% of patients, BCT was abnormal and proximal extension was observed in 41.8% of subjects. Attenuation correction (AC) findings in the upright and supine positions were attributed to frequencies of 20.5% and 25.2%, respectively. Weakly Acid (WA) findings in the upright and supine positions were abnormal in 50.9% and 49.5% respectively. Abnormal Non-Acid (NA) findings in the upright and supine positions were observed at 6.3 and 3.3 per cent. Mixed findings were abnormal in 61.9% and 65.4%, based on the upright and supine positions (Table 1).

Table 1: Frequency distribution of data based on various findings in patients

		Count	Layer N%
DeMeester Score	Abnormal	253	44.2%
Total Reflux time	Abnormal	260	45.5%
Number of Reflux	Abnormal	229	40%
Number of Long	Abnormal	138	24.1%
Longest Reflux	Abnormal	242	42.3%
BCT	Abnormal	15	2.6%
Proximal Extension	Pos	239	41.8%
Upright AC	Abnormal	117	20.5%
Supine AC	Abnormal	144	25.2%
Upright WA	Abnormal	291	50.9%
Supine WA	Abnormal	283	49.5%
Upright NA	Abnormal	36	6.3%
Supine NA	Abnormal	19	3.3%
Upright Mixed	Abnormal	354	61.9%
Supine Mixed	Abnormal	374	65.4%

SAP findings were related to the symptoms of the patient in 55.8% of the patients, while 30.2% of the patients had SAP findings without any association with the symptoms of the patient. They were also Results in 7% of cases were Pure Acid Reflux followed by Weakly Acid (1%), Non-Acid (0.3%), Mixed & Gas (5.2%), Functional (58.4%) and Esophageal Hypersensitivity (28%). Furthermore, Weakly Acid plus Acid was also found to be 8%, and Weakly Acid + Acid + Non-Acid were determined as 8.3% (Table 2).

Table 2: Frequency of diagnosis in patients

		Frequency	Per cent
Valid	Pure Acid Reflux	40	7
	Weakly Acid	6	1
	Non-Acid	2	0.3
	Mixed&Gas	30	5.2
	Functional	334	58.4
	Oesophagal	160	28
	Hypersensitivity		
	Total	572	100

Analysis of variance (ANOVA) did not show a significant difference in the frequency distribution of diagnosis based on the age of the patients ($P = 0.216$). The frequency distribution of diagnosis did not show a significant statistical relationship regarding gender-based on chi-square test ($P = 0.721$). The prevalence of functional conditions in men and women was revealed to be 59.1 and 57.6%, respectively while the cases of hypersensitivity were reported in 27.4% of men and 28.6% of women (Table 3).

Table 3: Distribution of diagnosis based on gender

		Diagnosis						Total
		Pure Acid Reflux	Weakly Acid	Non-Acid	Mixed&Gas	Functional	Oesophagal Hypersensitivity	
Gender	Female	19 (6.9%)	2 (0.7%)	2 (0.7%)	15 (5.4%)	159 (57.6%)	79 (28.6%)	276 (100%)
	Male	21 (7.1%)	4 (1.4%)	0	15 (5.1%)	175 (59.1%)	81 (27.4%)	296 (100%)
Total		40 (7%)	6 (1%)	2 (0.3%)	30 (5.2%)	334 (58.4%)	160 (28%)	572 (100%)

The frequency of diagnosis showed that the duration of symptoms was not statistically significant ($P = 0.429$) based on the ANOVA test.

Discussion

In this study, we investigated the various causes of GERD refractory in patients who were referred to Taleghani patient in Tehran from 2009 to 2017. All subjects in this study were Off PPI, meaning that patients did not take PPI and anti-acid for 2 weeks before testing. The test results showed that 7% of the cases belonged to Pure Acid Reflux based on 24 h pH-impedance, followed by Weakly Acid (1%), Non-Acid (0.3%), Mixed & Gas (5.2%), Functional (58.4%) and Esophageal Hypersensitivity (28%). Also,

Weakly Acid + Acid + Non-Acid cases were found to be 8.3%, where is the most common cause of refractory cases followed by hypersensitivity, which is consistent with other studies in this area [17]. These results are consistent with other studies in this area [17]. Penagini et al., (2015) evaluated 50 patients with refractory GERD in Italy. They determined that 15 of the patients (30%) had functional heartburn [18], while this rate was about 2 times higher in our research. In a cross-sectional study, Frazzoni et al., examined 80 patients with refractory GERD, 35% of them had functional heartburn [19], which was lower than the result of our study. In another study, Savarino et al. performed an analytical cross-sectional study in Italy with 219 patients suffering from refractory GERD that 39% had functional heartburn [20]. In the present study, this was higher which could be due to the 3-fold sample size.

Jung et al., (2007) in the United States, assessed 2298 patients with refractory GERD and found that 3% of men and 4% of women had suffered from functional disorders such as functional heartburn [21]. The results of the study are in agreement with the results of the current study. In another study by Savarino et al., 2009 found that 27% of patients with refractory GERD suffered from functional heartburn [22], which was half the amount, obtained in our study. The higher number of the present study can be because of the examination centre as a referral hospital. A cross-sectional study by Mohammed Khan et al. in 2014 found that almost 60% of patients with refractory PPIs NERD and SAP (+) had no acid reflux, and about half of nonerosive gastroesophageal reflux disease (NERD) patients on PPI had normal multichannel intraluminal impedance-pH (MII-pH) monitoring, which was equally divided into two groups: Functional Heart Burn and hyper-sensitive esophagus [23]. We did not find this equal ratio in our study, and the frequency of functional cases was higher. Herregods et al., reported in an analytical cross-sectional report that roughly one-third of patients referring to GERD symptoms have problems other than reflux, the most common of which is Functional Heart Burn. This justifies why these patients do not benefit from anti-acid therapy [24], and in our study, this is proven. Moreover, different studies on various subjects have published the regarding the above results [25] [26] [27] [28] [29].

In conclusion, our data suggest that more than half of GERD patients in the 24h pH-impedance analysis have functional disorders. Therefore, due to the high incidence of functional and hypersensitivity cases, we can treat the remaining cases according to the prevalence before making expensive and inaccessible tests. Taken together, it is recommended to use a treatment period for functional and hypersensitivity, such as selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, etc.).

References

1. Chen T, Lu M, Wang X, et al. Prevalence and risk factors of gastroesophageal reflux symptoms in a Chinese retiree cohort. *BMC Gastroenterol.* 2012; 12:161. <https://doi.org/10.1186/1471-230X-12-161> PMID:23153099 PMCID:PMC3573958
2. Sharma PK, Ahuja V, Madan K, Gupta S, Raizada A, Sharma MP. Prevalence, severity, and risk factors of symptomatic gastroesophageal reflux disease among employees of a large hospital in northern India. *Indian J Gastroenterol.* 2011; 30:128-34. <https://doi.org/10.1007/s12664-010-0065-5> PMID:21061110
3. Malfertheiner P, Hallerback B. Clinical manifestations and complications of gastroesophageal reflux disease (GERD). *Int J Clin Pract.* 2005; 59:346-55. <https://doi.org/10.1111/j.1742-1241.2005.00370.x> PMID:15857335
4. Wahlqvist P. Symptoms of gastroesophageal reflux disease, perceived productivity, and health-related quality of life. *Am J Gastroenterol.* 2001; 96:S57-61. [https://doi.org/10.1016/S0002-9270\(01\)02590-4](https://doi.org/10.1016/S0002-9270(01)02590-4)
5. Gisbert JP, Cooper A, Karagiannis D, et al. Impact of gastroesophageal reflux disease on work absenteeism, presenteeism and productivity in daily life: a European observational study. *Health Qual Life Outcomes.* 2009; 7:90. <https://doi.org/10.1186/1477-7525-7-90> PMID:19835583 PMCID:PMC2770561
6. Ciofica R, Gadenstätter M, Klingler A, Lechner W, Riedl O, Schwab GP. Quality of life in GERD patients: medical treatment versus antireflux surgery. *J Gastrointest Surg.* 2006; 10:934-9. <https://doi.org/10.1016/j.gassur.2006.04.001> PMID:16843863
7. Scholten T. Long-term management of gastroesophageal reflux disease with pantoprazole. *Ther Clin Risk Manag.* 2007; 3:231-43. <https://doi.org/10.2147/tcrm.2007.3.2.231> PMID:18360632 PMCID:PMC1936305
8. Wetscher GJ, Glaser K, Gadenstaetter M, Profanter C, Hinder RA. The effect of medical therapy and antireflux surgery on dysphagia in patients with gastroesophageal reflux disease without esophageal stricture. *Am J Surg.* 1999; 177:189-92. [https://doi.org/10.1016/S0002-9610\(99\)00011-2](https://doi.org/10.1016/S0002-9610(99)00011-2)
9. Fass R, Gasiorowska A. Refractory GERD: what is it? *Curr Gastroenterol Rep.* 2008; 10:252-7. <https://doi.org/10.1007/s11894-008-0052-5> PMID:18625135
10. Fass R. Functional heart burn. *Gastroenterol Hepatol.* 2014; 10:381-3.
11. Talaie R, Forootan M, Donboli K, et al. 24-hour ambulatory PH-metry in patients with refractory heartburn: a prospective study. *J Gastrointest Liver Dis.* 2009; 18(1):11-5. PMID:19337627
12. Forootan M, Ardeshiri M, Etemadi N, Maghssoodi N, Poorsaadati S. Findings of impedance PH-monitoring in patients with atypical gastroesophageal reflux symptoms. *Gastroenterol Hepatol Bed Bench.* 2013; 6:S117-S121. PMID:24834281 PMCID:PMC4017544
13. Mirbagheri SA, Sadeghi A, Amouie M, et al. Pyloric injection of botulinum toxin for the treatment of Refractory GERD accompanied with gastroparesis: a preliminary report. *Dig Dis Sci.* 2008; 53:2621-6. <https://doi.org/10.1007/s10620-007-0187-5> PMID:18256933
14. Ates F, Francis DO, Vaezi MF. Refractory gastroesophageal reflux disease: advances and treatment. *Expert Rev Gastroenterol Hepatol.* 2014; 8: 657-67. <https://doi.org/10.1586/17474124.2014.910454> PMID:24745809
15. Serra Pueyo J. Update on gastroesophageal reflux disease. *Gastroenterol Hepatol.* 2014; 37: 73-82. <https://doi.org/10.1016/j.gastrohep.2013.11.001> PMID:24355558
16. Haider SH, Kwon S, Lam R, et al. Predictive Biomarkers of Gastroesophageal Reflux Disease and Barrett's Esophagus in World Trade Center Exposed Firefighters: a 15 Year Longitudinal Study. *Sci Rep.* 2018; 8:3106. <https://doi.org/10.1038/s41598-018-21334-9> PMID:29449669 PMCID:PMC5814524
17. Pritchett, Jason M. Efficacy of esophageal impedance/PH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. *Clinical Gastroenterology and Hepatology.* 2009; 7: 743-8. <https://doi.org/10.1016/j.cgh.2009.02.022> PMID:19281866
18. Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D. Inconsistency in the Diagnosis of Functional Heartburn: Usefulness of Prolonged Wireless PH Monitoring in Patients with Proton Pump Inhibitor Refractory Gastroesophageal Reflux Disease. *J Neurogastroenterol Motil.* 2015; 21:265-72. <https://doi.org/10.5056/jnm14075> PMID:25843078 PMCID:PMC4398246
19. Frazzoni M, Conigliaro R, Mirante VG, Melotti G. The added value of quantitative analysis of on-therapy impedance-PH parameters in distinguishing refractory non-erosive reflux disease from functional heartburn. *Neurogastroenterol Motil.* 2012; 24(2):141-6, e87.
20. Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-PH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. *Dig Liver Dis.* 2011; 43:542-7. <https://doi.org/10.1016/j.dld.2011.01.016> PMID:21376679
21. Jung HK, Halder S, McNally M, et al. Overlap of gastro-oesophageal reflux disease and irritable bowel syndrome: prevalence and risk factors in the general population. *Aliment Pharmacol Ther.* 2007; 26:453-61. <https://doi.org/10.1111/j.1365-2036.2007.03366.x> PMID:17635380
22. Savarino E, Pohl D, Zentilin P, et al. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. *Gut.* 2009; 58:1185-91. <https://doi.org/10.1136/gut.2008.175810> PMID:19460766 PMCID:PMC2719081
23. Khan MQ, Alaraj A, Alsohaibani F., et al. Diagnostic utility of impedance-PH monitoring in refractory non-erosive reflux disease. *Journal of neurogastroenterology and motility.* 2014; 20: 497-505. <https://doi.org/10.5056/jnm14038> PMID:25273120 PMCID:PMC4204403
24. Herregods TV, Troelstra M, Weijnenborg PW., et al. Patients with refractory reflux symptoms often do not have GERD. *Neurogastroenterology Motility.* 2015; 27: 1267-73. <https://doi.org/10.1111/nmo.12620> PMID:26088946
25. Foroutan M, Loloie B, Irvani S, Azargashb E. Accuracy of rapid urease test in diagnosing *Helicobacter pylori* infection in patients using NSAIDs. *Saudi J Gastroenterol.* 2010; 16(2):110-112. <https://doi.org/10.4103/1319-3767.61238> PMID:20339181 PMCID:PMC3016498
26. Keshavarz MA, Moradi S, Emami Z, Rohani F. Association between serum 25(OH) vitamin D and metabolic disturbances in polycystic ovary syndrome. *Neth J Med.* 2017; 75(5):190-195. PMID:28653944
27. Forootan M, Tabatabaeefar M, Mosaffa N, Ashkalak HR, Darvishi M. Investigating Esophageal Stent-Placement Outcomes in Patients with Inoperable Non-Cervical Esophageal Cancer. *J Cancer.* 2018; 9(1):213-218. <https://doi.org/10.7150/jca.21854> PMID:29290788 PMCID:PMC5743730
28. Moradi S, Sahebi Z, Ebrahim Valojerdi A, Rohani F, Ebrahimi H. The association between the number of office visits and the control of cardiovascular risk factors in Iranian patients with type2 diabetes. *PLoS One.* 2017; 12(6):e0179190. <https://doi.org/10.1371/journal.pone.0179190> PMID:28666031 PMCID:PMC5493291
29. Zare Mehrjardi M, Bagheri SM, Darabi M. Successful ultrasound-guided percutaneous embolization of renal pseudoaneurysm by autologous blood clot: Preliminary report of a new method. *J Clin Ultrasound.* 2017; 45(9):592-596. <https://doi.org/10.1002/jcu.22462> PMID:28255997