Role of non-acid reflux in patients with non-erosive reflux disease

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Abstract
Non-erosive reflux disease (NERD) is the most common presentation of gastroesophageal reflux disease. Although acid reflux is the most important cause of symptom generation in NERD patients, non-acid reflux is also associated with reflux symptoms. The temporal relation between symptoms and reflux episodes is of importance in evaluating the results of combined pH-impedance monitoring in NERD patients. Mucosal hypersensitivity and mechanical stimulation due to great volume of non-acid reflux are among the putative mechanisms of symptom generation.

Keywords Non-acid reflux, non-erosive reflux disease

Introduction
Gastroesophageal reflux disease (GERD) is the most common reason for visiting an outpatient gastroenterology practice. It is estimated that in the United States approximately 40% of the adult general population experiences heartburn, the typical symptom of GERD at least once a week [1]. The spectrum of GERD includes: erosive reflux disease, characterized by the presence of typical reflux-related lesions in the distal esophagus; non-erosive reflux disease (NERD), characterized by abnormal distal esophageal acid exposure in the absence of endoscopically visible lesions in the distal esophagus; and hypersensitive esophagus (HE), characterized by a positive association between esophageal symptoms and gastro-esophageal reflux episodes in a patient with normal distal esophageal acid exposure and normal endoscopic findings in the distal esophagus [2]. In addition, patients with reflux symptoms, normal endoscopy, normal distal esophageal acid exposure and negative symptom association are thought to have functional heartburn according to the Rome III criteria [3]. NERD patients represent up to 60% of all patients with reflux symptoms. Heartburn is the typical symptom of NERD and the role of acid in its etiology is well established. Data suggesting that acid (pH<4) is important for reflux perception has been obtained from intra-esophageal instillation of solutions with increasing pH [4]. In this study, all subjects experienced pain with pH 1 and 1.5 solutions, 80% had pain with the pH 2 solution, and 50% had pain with solutions pH 2.5-6. The critical role of acid for triggering heartburn has since been confirmed by numerous clinical trials [5-7].

Thus, medical treatment of NERD patients is primarily based on a gastric acid suppressive drug, such as proton pump inhibitors (PPIs). Although PPIs are the most effective therapy for NERD, the response rates to PPIs treatment are lower in NERD patients compared to patients with erosive esophagitis [8]. In patients who do not respond to PPIs, ongoing symptoms may be caused by factors other than acid. Indeed, data from 24-h ambulatory pH monitoring have shown that more than 30% of NERD patients had normal distal esophageal acid exposure [9,10]. A recent review reported that, in patients with GERD who have reflux symptoms despite taking a PPI, more than 80% of reflux-related symptom episodes were associated with non-acid reflux (i.e. with pH>4) [11].

Detecting and quantifying non-acid reflux
Since conventional pH monitoring measures acid reflux by detecting drops in distal esophageal pH to below 4, this method is less accurate in detecting reflux episodes where the esophageal pH remains above 4 (i.e. non-acid reflux). Introduced in 2001 into clinical practice, multichannel intraluminal impedance is a new technique based on measurement of electrical conductivity
between multiple electrodes positioned along the axial length of a thin intraluminal probe. Impedance monitoring identifies retrograde bolus transit and can detect the physical properties of gastroesophageal reflux episodes (i.e., detect liquid, gas and mixed gas-liquid) reflux. However, it is not able to detect acidity of reflux contents thus, for clinical applications in the esophagus a pH electrode is incorporated into a combined impedance-pH monitoring catheter.

According to expert opinion, combined impedance-pH is currently the most accurate method for measuring reflux [12]. It allows the detection of all types of reflux and the characterization into acid and non-acid reflux; the latter can be subdivided in weakly acid and weakly alkaline reflux. Acid reflux has been defined as a reflux event associated with drop in esophageal pH <4, weakly acid when associated with a pH drop between 4 and 7 and weakly alkaline when reflux event is not associated with a pH drop <7 [12].

Establishing the temporal association between symptoms and reflux is very important and two methods are currently used; symptom index (SI) and symptom association probability (SAP). The SI is the percentage of symptom events preceded by a reflux episode within a 5-min time window. It is calculated by dividing the number of symptoms preceded by reflux by the total number of symptoms and expressed as percentage. The SI is considered positive when it is ≥50%. A SI for atypical symptoms (i.e., heartburn) ≥50% has a sensitivity of 93% and specificity to 71% for diagnosing acid reflux [13]. This index is limited by the fact that it does not take into account the total number of reflux episodes that actually occurred.

The SAP is calculated by dividing the total 24-h pH recording data into 2-min fragments. In each 2-min fragment, it is determined if there are reflux events and if there are reported symptoms. These data are then summarized into a 2x2 table. The association between reflux and symptoms is then calculated using Fisher’s exact test. A SAP ≥95% is considered positive and indicates that the probability of the association of reflux and symptoms occurring by chance is <5%. A positive SAP suggests that a patient’s symptoms are due to reflux. The relevance of both indices have been recently challenged by Slaughter et al who showed that SI and SAP values were largely determined by chance occurrences, unless patients with GERD refractory to PPI therapy have high rates of reflux [14]. Although these methodological short-comings could be kept in mind, analysis of symptom-reflux association is still useful in clinical practice.

**Mechanisms of symptom generation by non-acid reflux**

A recent review showed that weakly acidic reflux, pH [4-7], detected with impedance-pH is associated with regurgitation and atypical GERD symptoms [15]. Moreover, perfusion of bile salts into the esophagus at non-acidic pH can provoke heartburn [16]. Although the mechanism is unclear, short exposure of esophageal mucosa to bile acid in acidic and weakly acidic conditions can impair mucosal integrity in an experimental model [17]. Clinical studies have also reported that a proportion of patients with persistent reflux symptoms despite PPI therapy could be attributed to duodeno-gastro-esophageal reflux detected by esophageal bilirubin monitoring [18-20].

Another mechanism through which weakly acidic or weakly alkaline reflux is thought to generate symptoms is mechanical stimulation. Greater reflux volume can trigger heartburn irrespective of its acidity by distending the esophagus. Esophageal balloon distension commonly results in heartburn in patients with GERD [21,22]. Furthermore, the incidence of heartburn had increased in a linear fashion with increased balloon volume [21]. Pandolfino et al have showed anatomical degradation of the gastroesophageal junction in patients with GERD compared to controls, favoring the occurrence of volume reflux associated with transient lower esophageal sphincter relaxations [23,24].

Patients with NERD have less esophageal acid exposure but have greater esophageal sensitivity than patients with erosive esophagitis, perceiving less intense stimuli such as weakly acidic reflux [25]. Proximal esophageal extent of the refluxate is also associated with an increased likelihood of reflux symptoms. Zerbib et al demonstrated that weakly acidic and weakly alkaline reflux was as likely as acid reflux in the proximal esophagus to cause reflux symptoms [26]. In addition, the proportion of symptomatic reflux events in the proximal esophagus was greater compared to distal esophagus, irrespective of acidity [27]. Furthermore, a recent study showed that different reflux patterns may permit to classify NERD patients in various subgroups; patients with HE characterized by an increased number of acid and especially weakly acidic reflux events and by a higher rate of proximal reflux episodes [28].

**Clinical significance non-acid reflux**

In the current era of frequent PPI use, patients with reflux-like symptoms who do not respond to PPIs are the majority of GERD patients presented in outpatient gastroenterology practice. In those patients with ongoing symptoms despite acid suppression and normal endoscopy, it is desirable to perform reflux monitoring. Under these circumstances, combined impedance-pH represents the best tool of evaluation, because it detects both acid and non-acid reflux.

Evaluating only the positive evidence of symptom relationship with acid reflux events causes an underestimation of patients with real GERD and overestimation of patients with functional heartburn; using impedance-pH monitoring only 29% of patients were diagnosed with functional heartburn compared to 39% with pH alone [29]. A large multicenter study in 168 patients with persistent symptoms on PPI b.i.d. therapy found that 53 (37%) of the 144 patients who had symptoms during the study had a positive SI for non-acid reflux and 16 (11%) had a positive SI for acid reflux [30].
recent study confirmed that in 39% of patients on double daily PPI therapy non-acid reflux could be the cause of persistent symptoms [31]. A similar study using SAP found that 37% of patients had evidence of reflux-symptoms association; 17% for acid reflux, 5% for non-acid reflux and 15% for both acid and non-acid reflux [32]. Moreover, in patients with persistent symptoms on PPI therapy who had an esophageal acid exposure within the physiological range and a positive SI for reflux, a temporal relationship between non-acid reflux and symptoms was observed in the majority (77%) of these patients [33].

Fornari et al found that 57% of the total nocturnal reflux episodes were weakly acidic, raising a question about its clinical relevance [34]. Nocturnal sensitization of esophageal mucosa after exposure to damaging weakly acidic reflux might increase the occurrence of diurnal symptoms such as sour or bitter taste in the mouth [35]. In addition, presence of weakly acidic events may explain the difference in severity of esophagitis in patients with similar amount of acid reflux [36].

Although there are many studies that support the role of non-acid reflux as a cause of symptoms in NERD patients, especially those not responding to PPIs, there are no sufficient clinical outcome data for these patients. In a recent study, laparoscopic Nissen fundoplication was performed in 13 patients with GERD refractory to PPIs and with pathological acid exposure on pH monitoring; fundoplication similarly controlled acid and weakly acidic reflux [37]. Frazzoni et al reported good results in 38/40 patients with persistent GERD symptoms in whom pH-impedance monitoring demonstrated either abnormal numbers of reflux episodes or positive symptom association analysis [38].

Conclusions

Data support a role for non-acid reflux as a cause of symptoms in some NERD patients, especially those who do not respond to treatment with PPIs. Although refluxate with pH>4 is capable of triggering symptoms, responsible mechanisms are not fully elucidated. Greater esophageal sensitivity, large volume and proximal extent of refluxate are among the putative mechanisms. Combined impedance-pH is now considered the most sensitive test for reflux detection and it seems to have a critical role in establishing the relevance of non-acid in reflux-symptoms generation.

References

1. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101:2128-2138.
2. Savarino E, Zentilin P, Tutuian R, et al. The role of non-acid reflux in refining NERD: Lessons learned from impedance-pH monitoring in 150 patients off therapy. Am J Gastroenterol 2008;103:2685-2693.
3. Galmiche JP, Clouse RE, Balint A, et al. Functional esophageal disorders. Gastroenterology 2006;130:1459-1465.
4. Smith JL, Opekun AR, Larkai E, Graham DY. Sensitivity of the esophageal mucosa to pH in gastroesophageal reflux disease. Gastroenterology 1989;96:683-689.
5. DeMeester TR, Johnson LF, Joseph GJ, et al. Patterns of gastroesophageal reflux in health and disease. Ann Surg 1976;184:459-470.
6. Bredenoord AJ, Weusten BL, Curvers WL, et al. Determinants of perception of heartburn and regurgitation. Gut 2006;55:313-318.
7. Savarino E, Tutuian R, Zentilin P, et al. Characteristics of reflux episodes and symptom association in patients with erosive esophagitis and nonerosive reflux disease: study using combined impedance-pH off therapy. Am J Gastroenterol 2010;105:1053-1061.
8. Van Pixerlen B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastroesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2006;3:CD002095.
9. Watson RGP, Tham TCK, Johnston BT, et al. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux, the ‘sensitive esophagus’. Gut 1997;40:587-590.
10. Martinez SD, Malagon IB, Garewal HS, et al. Non-erosive reflux disease (NERD)-acid reflux and symptom patterns. Aliment Pharmacol Ther 2003;17:537-545.
11. Boeckxstaens GE, Smout A. Systematic review: role of acid, weakly acidic and weakly alkaline reflux in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2010;32:334-343.
12. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: Review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024-1031.
13. Singh S, Richter JE, Bradley LA, Haile JM. The symptom index. Differential usefulness in suspected acid-related complaints of heartburn and chest pain. Dig Dis Sci 1993;38:1402-1408.
14. Slaughter JC, Goutte M, Rymer JA, et al. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2011;9:868-874.
15. Sifrim D, Mittal R, Fass R, et al. Review article: acidity and volume of the refluxate in the genesis of gastro-oesophageal reflux disease symptoms. Aliment Pharmacol Ther 2007;25:1003-1005.
16. Siddiqui A, Rodriguez-Stanley S, Zubaidi S, et al. Esophageal visceral sensitivity to bile salts in patients with functional heartburn and in healthy control subjects. Dig Dis Sci 2005;50:81-85.
17. Farre R, van Malenstein H, De Vos R, et al. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. Gut 2008;57:1366-1374.
18. Bredenoord AJ, Weusten BL, Timmer R, et al. Characteristics of gastro-esophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. Am J Gastroenterol 2006;101:2470-2475.
19. Karamanolis G, Vanuytsel T, Sifrim D, et al. Yield of 24-hour esophageal pH and Bilitec monitoring in patients with persisting symptoms on PPI therapy. Dig Dis Sci 2008;53:2387-2393.
20. Gasiorowska A, Navarro-Rodriguez T, Wendel C, et al. Comparison of the degree of duodenogastroesophageal reflux and acid reflux between patients ho failed to respond and those who were successfully treated with a proton pump inhibitor once daily. Am J Gastroenterol 2009;104:2005-2013.
21. Takeda T, Nabae T, Kassab G, Liu J, Mittal RK. Oesophageal wall stretch: the stimulus for distension induced oesophageal sensation. Neurogastroenterol Motil 2004;16:721-728.
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22. Yang M, Li Z, Chen D, et al. Quantitative assessment and characterization of vis in patients with functional heartburn, non-erosive reflux disease, and erosive esophagitis. *Clin J Pain* 2010;26:326-331.

23. Pandolfino JE, Shi G, Trueworthy B, et al. Esophagogastric junction opening during relaxation distinguishes nonhernia reflux patients, hernia patients, and normal subjects. *Gastroenterology* 2003;125:1018-1024.

24. Pandolfino JE, Shi G, Curry J, et al. Esophagogastric junction distensibility: a factor contributing to sphincter incompetence. *Am J Physiol Gastrointest Liver Physiol* 2002;282:G1052-G1058.

25. Bredenoord AJ. Mechanisms of reflux perception in gastroesophageal reflux disease: a review. *Am J Gastroenterol* 2012;107:8-15.

26. Zerbib F, Duriez A, Roman S, Capdepong M, Mion F. Determinants of gastro-oesophageal reflux perception in patients with persistent symptoms despite proton pump inhibitors. *Gut* 2008;57:156-160.

27. Emerenziani S, Ribolsi M, Sifrim D, Blondeau K, Cicala M. Regional oesophageal sensitivity to acid and weakly acidic reflux in patients with non-erosive reflux disease. *Neurogastroenterol Motil* 2009;21:235-238.

28. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. *J Gastroenterol* 2012;47:159-168.

29. 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;43:542-547.

30. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy. A multicenter study using combined ambulatory impedance-pH monitoring. *Gut* 2006;55:1398-1402.

31. Sharma N, Agrawal A, Freeman J, et al. An analysis of persistent symptoms in acid-suppressed patients undergoing impedance-pH monitoring. *Clin Gastroenterol Hepatol* 2008;6:521-524.

32. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: A study in patients off and on therapy. *Am J Gastroenterol* 2006;101:1956-1963.

33. Viazis N, Keyoglou A, Kanellopoulos AK, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: A placebo controlled study using esophageal pH-impedance monitoring. *Am J Gastroenterol* 2012;107:1662-1667.

34. Fornari F, Blondeau K, Mertens V, Tack J, Sifrim D. Nocturnal gastroesophageal reflux revisited by impedance-pH monitoring. *J Neurogastroenterol Motil* 2011;17:148-157.

35. Poh CH, Allen L, Malagon I, et al. Riser’s reflux-an eye-opening experience. *Neurogastroentrot Motil* 2010;22:387-394.

36. Fiorucci S, Distrutti E, Di Matteo F, et al. Circadian variations in gastric acid and pepsin secretion and intragastric bile acid in patients with reflux esophagitis and in healthy controls. *Am J Gastroenterol* 1995;90:270-276.

37. Broeders JA, Bredenoord AJ, Hazebroek EJ, Broenders IAMJ, Gooszen HG, Smout AJPM. Effects of antireflux surgery on weakly acidic reflux and belching. *Gut* 2011;60:435-441.

38. Frazzoni M, Conigliaro R, Melotti G. Reflux parameters as modified by laparoscopic fundoplication in 40 patients with heartburn/regurgitation persisting despite PPI therapy: a study using impedance-pH monitoring. *Dig Dis Sci* 2001;56:1099-1106.