

# 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

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## 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].

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## 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  $\geq 50\%$ . A SI for atypical symptoms (i.e. heartburn)  $\geq 50\%$  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-gastroesophageal 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 outpatients 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]. A

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.

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