Management of Patients With Functional Heartburn

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Heartburn is a symptom synonymous with gastroesophageal reflux disease (GERD), but as our knowledge advances, we find that GERD is a more complex disorder than was originally thought. First, it is known that almost two-thirds of those with typical heartburn do not have erosions and this condition—nonerosive reflux disease (NERD)—is a heterogeneous disorder. With the advent of pH impedance testing, it is further recognized that NERD consists of 3 phenotypes, namely, true NERD, hypersensitive esophagus (with Rome IV, it is now termed reflux hypersensitivity) and functional heartburn (Figure 1). The Rome IV diagnostic criteria for functional heartburn is given in Table 1.

So, how common is functional heartburn? Because the term was recently introduced and the condition requires a normal endoscopy and normal reflux testing, there is a paucity of epidemiology data. Available case series from the West indicated a prevalence between 21.5% and 49.6%, but a lower prevalence has been reported in the Asian series, between 11.5% and 37.4% (Supplementary Table 1). A population-based study from Australia using the Rome II criteria reported a prevalence of 10.4%. Long-term outcome data are limited, but many patients remain symptomatic for a long time with a benign course.

Do We Understand the Pathophysiology?

In many functional gastrointestinal (GI) disorders, including functional heartburn, the actual mechanisms remain unclear although sensitization of the gut–brain axis seems to be important. Esophageal hypersensitivity can be in the form of allodynia (nonpainful stimuli being painful) or hyperalgesia (painful stimuli being amplified). Central sensitization occurs because of psychological and cognitive factors that heighten the heartburn perception. Peripheral sensitization arises from esophageal luminal factors (chemical or mechanical) that sensitize the visceral afferents. With the Rome IV criteria, reflux hypersensitivity is separated out from NERD (Rome III) and functional heartburn (Rome II). It is characterized by sensitivity to physiologic amounts of gastroesophageal reflux (both acid and nonacid). In contrast, functional heartburn is more sensitized to mechanical stimuli, for example, gas in the refluxate rather than acid stimuli with about a quarter having a negative acid perfusion test.¹ There is also a lack of mucosal changes in functional heartburn, demonstrated both histologically and with mucosal impedance measurement. Rather than direct injury, it is now believed that low-grade microinflammation with subsequent cytokine-mediated neuroimmunologic effects is probably the main mechanism of peripheral sensitization.² Psychological disturbance can exacerbate heartburn, for example, based on a longitudinal study, the presence of severe and sustained stress predicted increased heartburn.³ Cortical-evoked potential responses from distension and acid perfusion were also found greater in patients with

![Figure 1. Functional heartburn is an entity in the spectrum of gastroesophageal reflux disease (GERD) with the least acid exposure time (AET) and symptom association index. Differences of functional heartburn from other phenotypes in the GERD spectrum are listed in the table. PPI, proton pump inhibitor; NERD, nonerosive reflux disease; SI, symptom association index.](https://doi.org/10.1053/j.gastro.2018.04.030)
How to Identify Functional Heartburn

The typical patient is a young or middle-aged woman with a long history of heartburn. Approximately two-thirds of patients remain symptomatic for >2 years. Symptom severity and impairment in health-related quality of life with functional heartburn are very similar to any other GERD phenotypes. Patients often consult when their symptoms are refractory to proton pump inhibitors (PPIs), but reported rates of refractory heartburn could vary significantly, because of the arbitrary definition of PPI failure. In Asia, refractory GERD is considered if symptom is unresponsive to 8 weeks of a standard dose of PPI. In nonrandomized primary care trials, the reported prevalence of persistent troublesome heartburn despite PPI was 17% and in randomized trials it was 32%. Functional heartburn is present in approximately one-half of PPI nonresponders and one-quarter of PPI responders.

A management algorithm for heartburn is shown in Figure 2. In the presence of alarm features (including dysphagia, weight loss, anemia, and a family history of esophageal cancers), patients would be referred for further investigations, including an upper endoscopy examination, which in functional heartburn should be normal, without erosions or Barrett’s esophagus or adenocarcinoma. Hiatal hernia is an uncommon finding in functional heartburn. It is also important to exclude eosinophilic esophagitis and gastric inlet patch. Increasingly recognized for the past 2 decades, eosinophilic esophagitis may overlap with GERD and, not surprisingly, with functional heartburn as well, because hypersensitivity is a recognized mechanism in eosinophilic esophagitis. In contrast, gastric inlet patch may be acid secretory and, therefore, it can produce oropharyngeal and heartburn symptoms. Conventional white light endoscopy is limited when it comes to minimal changes in the esophageal mucosa, and newer technology of enhanced imaging and endomicroscopy may allow better detection of mucosal and cellular changes seen in NERD and, therefore, its differentiation from functional heartburn. Other biomarkers may be available in the future to help differentiate between the 2 conditions for example amino (N)-terminal fragments of e-cadherin, which helps to maintain the integrity of intercellular junctions.

Although ambulatory reflux testing is not readily available, this test is performed off PPI and allows for the differentiation between GERD phenotypes based on reflux burden and symptom association. With functional heartburn, first, the reflux burden must be normal with esophageal acid exposure time of <4%. However, it is known that normative values for acid exposure time may vary with approximately 30% of false-negative rates in reflux esophagitis. Second, a positive symptom association index denotes reflux hypersensitivity and, if negative, denotes functional heartburn; however, it must be borne in mind that symptoms perceived can be subjective and not all symptoms are captured in a 24-hour study. Owing to its better sensitivity in the detection of symptoms association with acid reflux, a wireless pH capsule study over 96 hours is preferred, although it is expensive. If reflux testing is performed on PPI for patients with confirmed GERD (ie, with grade C or D erosive esophagitis or Barrett esophagus), and the reflux testing results are negative, then it means that functional heartburn is overlapped with GERD. Belching and
ruminations, both associated with reflux, are other differentials in PPI-refractory heartburn.

Two additional impedance-based parameters may be useful to distinguish functional heartburn from NERD, namely, mean nocturnal baseline impedance (MBNI) and postreflux swallow-induced peristaltic wave (PSPW). MBNI consists of measuring the baseline impedance 3 or 5 cm above the lower esophageal sphincter during an overnight rest as the mean baseline impedance of three 10-minute time periods in a period without swallowing. MNBI is lower among PPI-responsive than PPI-refractory functional heartburn.

Recently, an endoscopic-guided probe that allows the real-time measurement of mucosal admittance could distinguish GERD from functional heartburn in a similar fashion to MNBI, with GERD having a higher mucosal admittance value than functional heartburn. In contrast, PSPW, a marker of chemical clearance, is defined as an antegrade 50% decrease in impedance relative to the pre-swallow baseline impedance from the most proximal sites reaching all distal sites, followed by a ≥50% return to baseline in all distal sites. PSPW index is number of refluxes followed within 30 seconds by a PSPW divided by total number of refluxes. The index is found lower among NERD compared with functional heartburn. These tools are exploratory at this time, and they require further studies to evaluate their efficacies over acid exposure time and symptom association.

Esophageal hypersensitivity can be further investigated with balloon distension or acid perfusion studies, but such tests are only available at specialized centers. Concomitant hypotensive esophagogastric junction, hiatal hernia, impaired peristaltic integrity, and or other major motility disorders (15%-20%) need to be excluded by high-resolution manometry testing. Features to suggest functional heartburn over GERD include the presence of other functional GI disorders (including functional chest pain, functional dyspepsia, and irritable bowel syndrome) and psychological comorbidities (including depression, anxiety, and somatization). Overlap of heartburn with other bowel symptoms should be sought during history taking. Consults with a psychologist or psychiatrist will be helpful if disturbed psychological well-being is found.

How to Manage Functional Heartburn

Lifestyle changes are commonly advised, but they have limited evidence and therapeutic responses. Such changes may include avoidance of certain foods (fat, spices, fizzy drinks), avoidance of large and late meals, weight loss, and postural change during sleep.

Antisecretory therapy is often prescribed in practice, but because the acid burden is not the main feature, we do not expect a response rate beyond 50% in true functional heartburn unless if functional heartburn overlaps with GERD. For the same reason, antireflux surgery is not going to help these patients. In PPI-refractory heartburn, reflux testing off PPI may help to guide therapy by de-escalating PPI in those with a diagnosis of functional heartburn.

Although a placebo effect is possible, in some other patients with functional heartburn, antisecretory therapy with or without alginate may help to decrease any acid and or nonacid (bile or pepsin) exposure that occurs at the esophagus where chemical or reflux hypersensitivity is predominant. In addition, the use of ranitidine in functional heartburn has been found to improve sensory parameters after acid infusion but not distension, and the authors postulated that H2RA receptors in the esophagus might actually modulate heartburn thresholds.

There are otherwise limited studies for other pharmacologic agents specifically for functional heartburn. For those who failed antisecretory therapy, agents that improve esophageal hypersensitivity can be tried and neuromodulators are commonly used to achieve this. The choice of neuromodulators is often governed by experience from other functional GI diseases. Neuromodulators would be especially helpful in the presence of a positive balloon distension test (Figure 2). These neuromodulators may include tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and trazodone. For example, fluoxetine given over 6 weeks was superior to omeprazole and placebo in improving heartburn. There is also some evidence of efficacy for 5-hydroxytryptamine3 antagonists and 5-hydroxytryptamine4 agonists, for example, tegaserod, which decreased heartburn after distension but not acid infusion. When prescribing these drugs, side effects and compliance issues should be kept in mind.

Antidepressants may also be helpful if central sensitization and or psychological disturbances are evident. Not all behavioral therapies have documented success in functional heartburn; for example, although esophageal-directed hypnotherapy seemed to work for functional heartburn, biofeedback did not. Other functional GI disorders should be sought, evaluated, and treated. Although evidence is limited, a psychology consult is always helpful when all the other therapeutic options have been exhausted (Figure 2).

Conclusions

Functional heartburn is recognized as a separate entity in the GERD spectrum of disorders. The exact pathophysiologic mechanisms of this entity remain to be elucidated. Reflux testing allows us to differentiate functional heartburn from other phenotypes; however, better markers are needed. Treatment options are limited by evidence but neuromodulators and or psychological interventions are needed to address the gut–brain axis disturbance associated with this disease entity.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.04.030.

References

1. Shapiro M, Green C, Bautista JM, et al. Functional heartburn patients demonstrate traits of functional bowel disorder but lack a uniform increase of chemoreceptor...

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Conflicts of interest
The authors disclose no conflicts.

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**Supplementary Table 1. Summary of Reported Epidemiology of Functional Heartburn**

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Method</th>
<th>Sample Size</th>
<th>Prevalence of FH, n (%)</th>
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<td><strong>Western series</strong></td>
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<td>reflux symptoms 32 (21.5)</td>
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</table>

**References**


1. Typical features of functional heartburn includes
   a. male sex
   b. severity of symptoms is similar to that of typical GERD patients
   c. never responds to PPI
   d. typically presents with extraesophageal complications of reflux

**True or False**

2. Functional heartburn is a subtype of NERD (non-erosive reflux disease)

3. Patients with functional heartburn typically have a negative symptom association index on esophageal pH testing

4. A diagnosis of functional heartburn requires evidence of normal esophageal acid exposure and no esophageal motor disorder

5. H2RA may play a role in the management of functional heartburn by modulating heartburn thresholds

6. Mean nocturnal baseline impedance is lower in patients with functional heartburn

7. Functional heartburn is worsened more by mechanical stimuli than acid stimuli

8. Acid reducing therapy has no role in the management of functional heartburn