Update on Functional Heartburn

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Abstract: The definition of functional heartburn has been refined over the years. It is currently described, based upon Rome IV criteria, as typical heartburn symptoms in the presence of normal upper endoscopy findings (including normal biopsies), normal esophageal pH testing, and a negative association between symptoms and reflux events. Functional heartburn is very common, affecting women more than men, and with reflux hypersensitivity makes up the majority of heartburn patients who fail twice-daily proton pump inhibitor therapy. These disorders overlap with other functional gastrointestinal disorders and are often accompanied by psychological comorbidities. Diagnosis is made by using endoscopy with esophageal biopsies, wireless pH capsule, pH-impedance monitoring, and high-resolution esophageal manometry. Additional diagnostic tools that may be of value include magnification endoscopy, chromoendoscopy, narrow-band imaging, autofluorescence imaging, mucosal impedance, impedance baseline values, and histopathology scores. Functional heartburn is primarily treated with neuromodulators. Psychological intervention and complementary and alternative medicine may also play important roles in the treatment of these patients.

The term functional heartburn was introduced relatively recently and appeared for the first time in publications in the late 1980s through the early 1990s.[1,2] The introduction of the term functional heartburn to clinical practice was a major breakthrough in understanding and managing heartburn symptoms, especially of patients who had failed proton pump inhibitor (PPI) treatment.[3] In addition, it was recognized that esophageal symptoms are not stimulus specific and, thus, not only esophageal acid exposure can lead to heartburn.[4]

The recently published Rome IV criteria have introduced 2 functional esophageal disorders with heartburn as the predominant symptom, functional heartburn and reflux hypersensitivity (Table 1).[5] The main impact of Rome IV on functional esophageal disorders was the recognition that reflux hypersensitivity, formerly known as hypersensitive esophagus, is a separate disorder. What differentiates

**Table 1.** Rome IV Functional Esophageal Disorders

- Functional chest pain
- Functional heartburn
- Reflux hypersensitivity
- Globus
- Functional dysphagia

functional heartburn from reflux hypersensitivity is the presence of symptoms that correlate with gastroesophageal events in patients with reflux hypersensitivity.

The definition of functional heartburn has evolved from one Rome meeting to another. Recognizing this evolution will help us understand the current Rome IV definition of functional heartburn. Rome II proposed that patients with heartburn and normal endoscopy findings should be divided into patients with nonerosive reflux disease (NERD) (abnormal esophageal acid exposure) and patients with functional heartburn (normal esophageal acid exposure). However, based on Rome II criteria, the functional heartburn group was composed of patients with reflux hypersensitivity (hypersensitive esophagus) and patients with heartburn unrelated to reflux.[1]

Rome III also suggested that patients with heartburn and normal endoscopy findings should be divided into patients with NERD and patients with functional heartburn.[2] Unlike in Rome II, the functional heartburn group had to demonstrate normal upper endoscopy findings, normal pH testing, a lack of symptom association with reflux events, and no response to antireflux treatment. The NERD group included patients with abnormal esophageal acid exposure, patients with reflux hypersensitivity, and patients with similar characteristics as those with functional heartburn but who do respond to antireflux treatment. Rome IV included 3 disorders under the category of patients with heartburn and normal endoscopy findings: NERD, functional heartburn, and reflux hypersensitivity (Figure 1).[5]

As a group, functional esophageal disorders are characterized by the presence of chronic symptoms attributed to the esophagus in the absence of structural, inflammatory, motor, or metabolic disorders. According to the Rome IV criteria, the diagnosis of a functional esophageal disorder requires having symptoms for the past 3 months with symptom onset at least 6 months before diagnosis. Nonesophageal causes for symptoms should be excluded first before the esophageal etiology is considered.
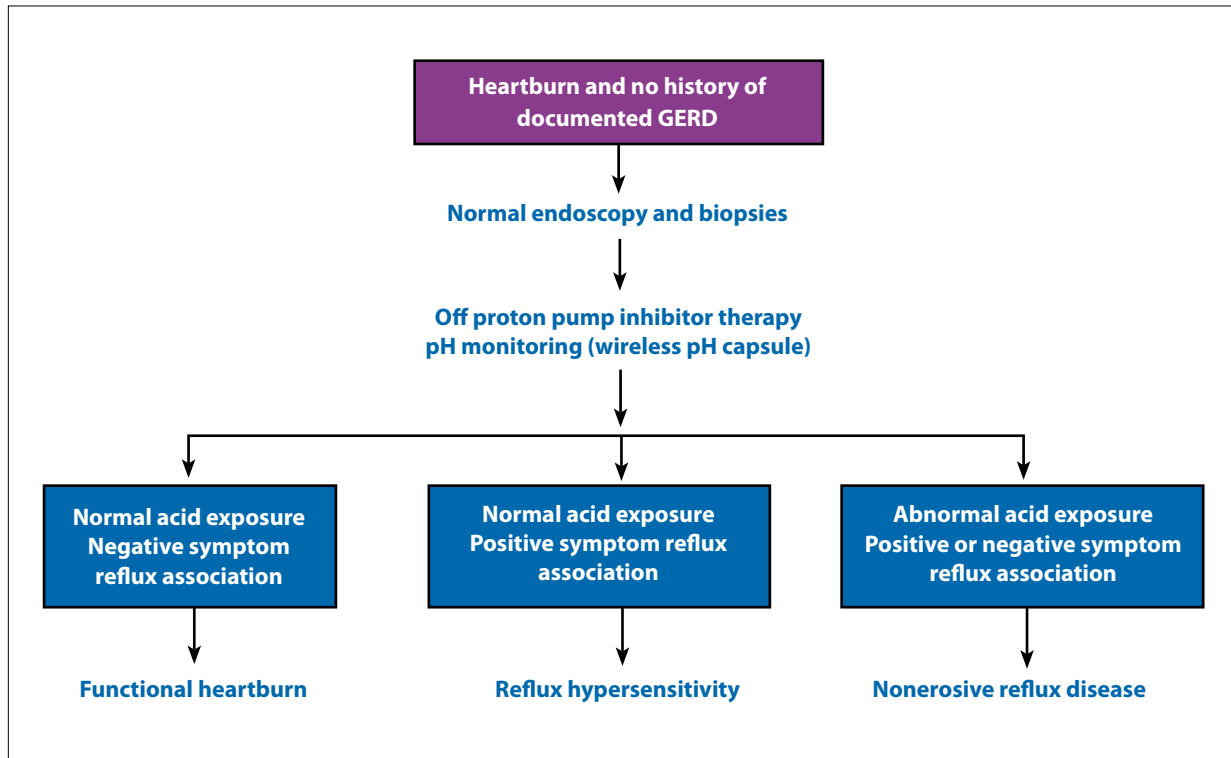
Figure 1. Classification of patients with normal endoscopy findings and no history of documented gastroesophageal reflux disease (GERD) using Rome IV criteria.

Table 2. Diagnostic Criteria[a] for Functional Heartburn (Rome IV)

Must include all of the following:
• Burning retrosternal discomfort or pain
• No symptom relief despite optimal antisecretory therapy
• Absence of evidence that gastroesophageal reflux disease (elevated acid exposure time and/or symptom reflux association) or eosinophilic esophagitis is the cause of the symptom
• Absence of major esophageal motor disorder (achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm, jackhammer esophagus, absent contractility)

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis and a frequency of at least twice a week.

Gastroesophageal reflux disease (GERD), major esophageal motor disorders, and eosinophilic esophagitis may be responsible for chronic heartburn symptoms. Hence, it is imperative that these conditions be ruled out before a diagnosis of any of the aforementioned functional esophageal disorders is established. Although benign in nature, functional esophageal disorders, including functional heartburn and reflux hypersensitivity, cause considerable impairment in quality of life and result in a significant economic burden on the health care system. Additionally, the limited understanding of the pathophysiologic basis of these conditions commonly results in frustration for both patients and physicians. Moreover, therapies are mainly empiric in nature and, in many cases, of limited value.

Definition

Functional heartburn has been defined by Rome IV criteria as burning retrosternal discomfort or pain in patients who demonstrate a lack of symptom relief despite optimal antisecretory therapy in the absence of evidence of GERD, eosinophilic esophagitis, a major esophageal motor disorder (achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm, jackhammer esophagus, and absent contractility), or structural abnormality.[6] These criteria must be fulfilled for the previous 3 months, with symptom onset at least 6 months before diagnosis and a frequency of at least twice a week (Table 2).

In summary, the definition of functional heartburn has evolved over the years. In Rome II, functional heartburn included patients with reflux hypersensitivity. In Rome III, these patients were placed under NERD, and, consequently, the definition of functional heartburn

evolved to specifically denote patients with heartburn that is not related to gastroesophageal reflux.[2] Rome IV essentially maintained the definition of functional heartburn from Rome III.

Epidemiology

As with all other functional esophageal disorders, the prevalence of functional heartburn in the general population remains to be elucidated. Early studies from tertiary referral centers suggested that approximately 50% of the patients presenting with heartburn have erosive esophagitis on upper endoscopy.[7,8] However, later studies that were performed in the community setting revealed that up to 70% of these patients have normal endoscopy findings.[9] Originally, these patients were all considered to have NERD. Later, it was demonstrated that patients with heartburn and normal endoscopy findings are in fact a heterogeneous group. Further subcategorization of these patients relies primarily on the results of esophageal pH monitoring. Approximately half of the patients who have normal endoscopy findings also demonstrate normal esophageal acid exposure during esophageal pH monitoring.[10] Furthermore, 40% of those with normal endoscopy findings and normal pH test results have reflux hypersensitivity (a positive correlation between symptoms and reflux events), and 60% have functional heartburn.[10] Thus, functional heartburn accounts for 21% of all untreated patients presenting with heartburn (Figure 2).[11] One study assessed 329 endoscopy-negative patients with pH-impedance monitoring off PPI treatment.[12] By using Rome III criteria, the authors demonstrated that 40% of the patients had NERD, 36% had reflux hypersensitivity, and 24% had functional heartburn. However, an earlier retrospective study had demonstrated that 38% of the patients had reflux hypersensitivity and 29% had functional heartburn.[13] In patients with refractory heartburn who failed twice-daily PPIs, the prevalence of functional heartburn can reach 52% to 54%.[14] In one study, 43 of 78 PPI-nonresponder patients (55%) who underwent 24-hour pH-impedance monitoring while on twice-daily PPIs were found to have functional heartburn.[15]

The demographics of patients with functional heartburn have been scarcely studied. When compared to patients with NERD, those with functional heartburn have the same female predominance and mean age (46 years).[16] The range of *Helicobacter pylori* infection is between 30% and 45%, and hiatal hernia is very uncommon (20%). There is no difference in symptom characteristics between functional heartburn and NERD except for a longer history of heartburn in patients with functional heartburn. Overall, concomitant functional bowel or other gastrointestinal (GI) disorders, such as functional
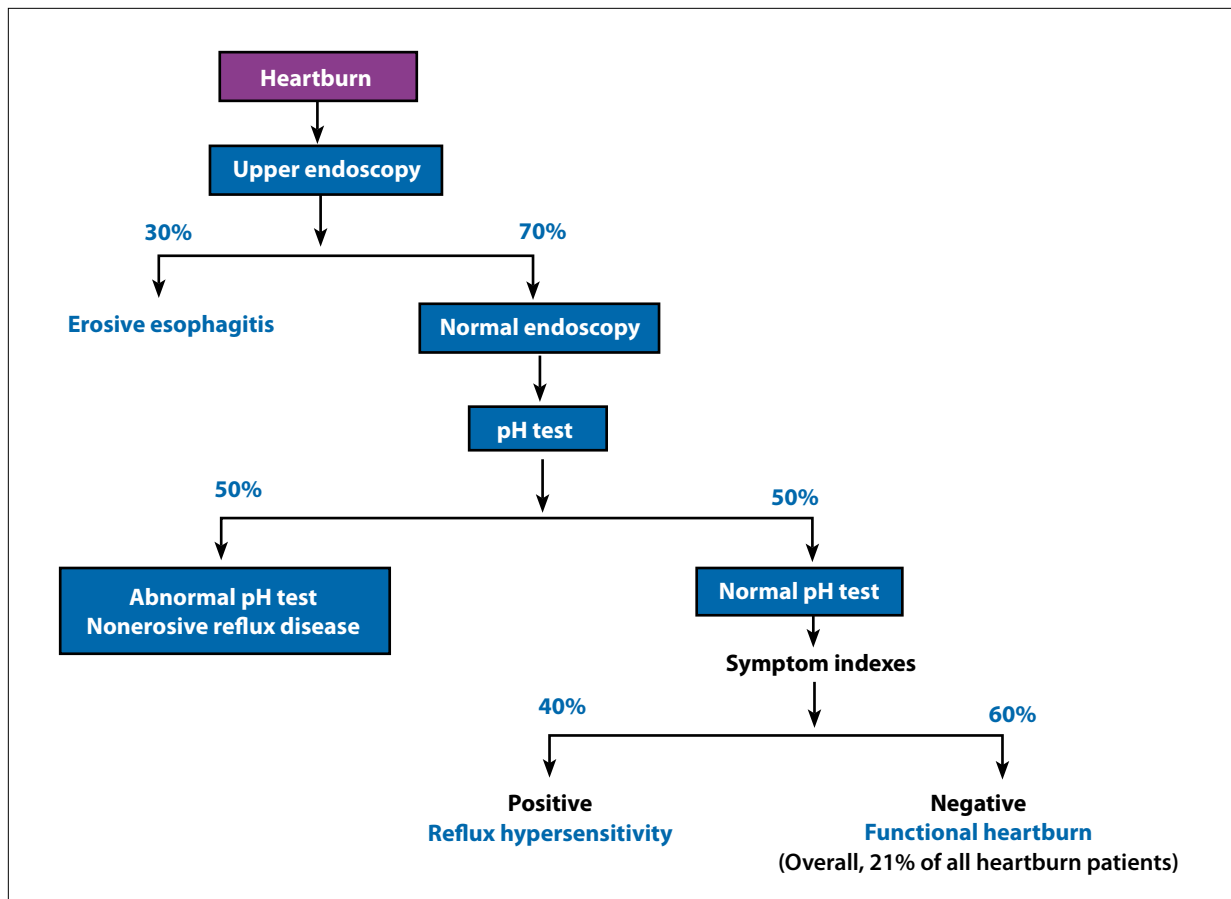
Figure 2. Percentage of functional heartburn patients among patients with normal endoscopy findings.

Reproduced with permission from Yamasaki T, Fass R.[11]

chest pain, functional dyspepsia, and irritable bowel syndrome (IBS), are relatively common in both disorders.[17-19] Importantly, dyspeptic symptoms (postprandial fullness, bloating, early satiety, and nausea) are significantly more common in functional heartburn as compared to NERD or reflux hypersensitivity.[17] Several studies have emphasized that IBS symptoms are strong predictors of heartburn severity in patients with functional heartburn.[20,21] In general, the psychological profile of functional heartburn patients is similar to that of NERD patients except for an increase in reports of somatization.[16] However, a study claimed that major depressive disorders were significantly more common in functional heartburn patients as compared with NERD patients.[22] A recent study suggested that psychological factors may drive the overlap between functional GI disorders, such as functional heartburn with functional dysphagia.[23]

The natural course of patients with functional heartburn remains unknown. In a study that followed 40 patients who fulfilled the criteria of functional heartburn, the authors demonstrated that 22 months after diagnosis,

66% of the patients were still experiencing heartburn.[24] The study suggests that functional heartburn is a chronic and durable disorder in the majority of patients.

Pathophysiology

Repeated studies in patients with functional heartburn who underwent either esophageal balloon distention or electrical stimulation have consistently demonstrated lower perception thresholds for pain compared with those in patients with other phenotypic presentations of GERD.[25-27] Furthermore, objective neurophysiologic measures of esophageal-evoked potential latency revealed that functional heartburn patients achieve equivalent esophageal sensitivity.[28] By contrast, stimulus response functions to acid perfusion in patients with functional heartburn gave mixed results. Rodriguez-Stanley and colleagues[29] reported that 90% of patients with functional heartburn experienced abnormal responses to esophageal balloon distention, intraesophageal acid perfusion (Bernstein test), or both. Yang and colleagues[26] reported that

patients with functional heartburn are more sensitive to mechanical and chemical stimuli than NERD patients. Thoua and colleagues[30] have demonstrated increased esophageal sensitivity in patients with functional heartburn compared with patients with NERD or erosive esophagitis. On the other hand, Shapiro and colleagues[16] demonstrated a higher mean value for time to heartburn symptoms and lower mean values for intensity and acid perfusion sensitivity scores than patients with NERD. Additionally, one-quarter of patients with functional heartburn had a negative acid perfusion test. This latter study was done using the Rome II criteria, at that time supporting the hypothesis that functional heartburn is composed of a heterogeneous group of patients. Another small study compared esophageal acid sensitivity and mucosal integrity (using electrical tissue impedance spectroscopy) between patients with functional heartburn and those with NERD.[31] The authors found that patients with functional heartburn did not show esophageal acid hypersensitivity as seen in NERD patients despite having similar esophageal mucosal integrity.

Increased mechanoreceptor sensitivity to balloon distention seems to be a general phenomenon in functional heartburn; in contrast, only a subset of patients show increased chemoreceptor sensitivity to acid. Overall, it appears that esophageal hypersensitivity is an important underlying mechanism for symptom generation in functional heartburn.[32]

Central neural mechanisms,[33,34] such as psychological comorbidity (anxiety and depression) stress, hypervigilance, and sleep deprivation, can modulate esophageal perception and cause patients to perceive low-intensity esophageal stimuli as being painful. However, it is still unclear what role these central factors play in symptom generation of patients with functional heartburn. Yang and colleagues[27] have demonstrated that cortical-evoked potential responses resulting from esophageal distention and acid perfusion were greater in patients with functional heartburn than in controls. The authors suggested that visceral neural pathway dysfunction and/or alteration in central processing may precipitate esophageal hypersensitivity in functional heartburn patients.[27] Frazzoni and colleagues[35] evaluated patients with different phenotypic presentations of GERD and compared them with functional heartburn patients and normal controls. Patients with functional heartburn did not differ from normal controls in their distal esophageal acid exposure profile, prevalence of hiatal hernia, distal esophageal amplitude contraction, and lower esophageal sphincter basal pressure. This study suggests that mechanisms other than reflux are likely to have an important role in symptom generation of patients with functional heartburn. Martinez and colleagues[36] demonstrated that

patients with NERD were more likely to have a symptom index greater than 75% than functional heartburn and reflux hypersensitivity patients together (61.9% vs 10.5%; P=.0001). In the functional heartburn group, patients reported having heartburn at a pH of less than 4 only 12.7% of the time compared with 70.7% of the time in those with reflux hypersensitivity despite a similar mean number of heartburn episodes.[36]

Several local factors have been suggested to play an important role in symptom generation of patients with functional heartburn. Cicala and colleagues[37] have demonstrated that patients with functional heartburn (per Rome II criteria) have the highest proximal acid exposure that is associated with heartburn compared with that in patients with NERD or erosive esophagitis. However, when Rome III criteria were used, the rate of proximal reflux events in NERD and reflux hypersensitivity patients was significantly greater than the rate in functional heartburn patients and healthy controls.[12,38] Proximal migration of esophageal acid exposure has been shown to be an important factor in symptom generation of GERD patients, specifically in those with functional heartburn.[39,40]

Dilated intercellular spaces, a common histopathologic finding in all GERD patients that has recently appeared not to be essential for sensory afferents sensitization, have been observed in patients with heartburn and normal esophageal acid exposure.[41] However, using Rome II criteria, these studies[37,39,41] included the reflux hypersensitivity group under functional heartburn. Further research assessing only true functional heartburn patients demonstrated that the diameter of dilated intercellular spaces in these patients is similar to that of normal controls.[5] pH-impedance studies did not find any difference in the degree of weakly acidic reflux between functional heartburn (Rome II) and the different GERD groups.[40,42] However, the presence of gas in the refluxate appears to enhance reflux perception in functional heartburn patients[42] and those with reflux hypersensitivity. Baseline impedance levels were found to be similar when functional heartburn patients were compared with healthy controls.[43]

Oxidative DNA damage to the epithelial cells of the esophagus has been shown to occur after acid exposure. A subset of functional heartburn patients (Rome II criteria) demonstrates this immunohistochemical abnormality.[44] It is yet to be determined whether these are primarily reflux hypersensitivity patients.

Shapiro and colleagues[16] have suggested that functional heartburn patients demonstrate traits of a functional bowel disorder. The authors have shown increased reports of chest pain and somatization by patients as well as alteration in autonomic function.

Table 3. Clinical Characteristics of Patients With Functional Heartburn

• More common in women than in men
• Middle age
• Long history of heartburn
• Symptom severity and frequency similar to those of GERD phenotypes
• Concomitant functional gastrointestinal disorder (functional chest pain, functional dyspepsia, irritable bowel syndrome)
• May overlap with GERD
• Esophageal dysmotility: rare
• Hiatal hernia: uncommon
• Health-related quality of life similar to that of other GERD phenotypes
• Psychological comorbidity (depression, anxiety, somatization)

GERD, gastroesophageal reflux disease.

Clinical Presentation

In general, the clinical presentation of functional heartburn does not differ from the clinical presentation of NERD or any other GERD phenotype. Heartburn severity and frequency are similar in both groups.[45,46] In addition, both disorders affect primarily young and middle-aged women and are associated with other functional GI disorders such as functional chest pain, functional dyspepsia, and IBS.[47] Also, psychological comorbidities, including depression, anxiety, and somatization, are not uncommon in both groups of patients.[16] The concomitant presence of other functional GI disorders may result in other GI symptoms in patients with functional heartburn. However, the prevalence of other non-GI–related functional or nonfunctional symptoms is not known. Shapiro and colleagues[16] compared the clinical characteristics of patients with functional heartburn vs those with NERD. The authors found no statistical differences in demographics, frequency of hiatal hernia, and prevalence of *H pylori* infection between the 2 groups. However, patients with functional heartburn had a significantly longer history of heartburn and reported more episodes of chest pain than NERD patients (7.5 years and once a week vs 3.5 years and once a month, respectively; *P*<.005). Although there was no difference in reported quality of life, patients with functional heartburn scored significantly higher in the somatization domain than patients with NERD. Table 3 summarizes the overall clinical characteristics of patients with functional heartburn.

Diagnosis

Establishing the diagnosis of functional heartburn requires 2 invasive procedures: upper endoscopy and reflux monitoring.[24] Various advanced endoscopic imaging techniques have been suggested to distinguish between NERD and functional heartburn patients (abnormal vs normal findings, respectively, in patients with heartburn), such as high-magnification endoscopy, narrow-band imaging, and autofluorescence imaging endoscopy.[48,49] The yield of random distal esophageal biopsies to assess for the presence of typical GERD-related histopathologic findings and, thus, improve diagnosis of GERD is very low.[50] However, recent research has suggested that biopsies from the distal part of the esophagus can differentiate between GERD and functional heartburn by documenting certain, or a combination of, histopathologic changes that are consistent with GERD but are not found in patients with functional heartburn.[51] For example, the presence of a normal diameter of intercellular spaces in the context of heartburn symptoms suggests functional heartburn.[52] Furthermore, an increase in the diameter of dilated interepithelial spaces and an increase in the histologic sum score (adding the individual scores of papillary elongation, basal cell hyperplasia, dilated interepithelial spaces, and inflammation) have been shown to be the most important variables that differentiate functional heartburn from NERD.[53]

Performing reflux monitoring after a normal upper endoscopy is pivotal for further evaluation for the presence of functional heartburn. Having a negative pH test or pH-impedance study is required for diagnosis, but what separates reflux hypersensitivity and functional heartburn is the presence of a negative correlation between symptoms and reflux events using the symptom index and/or symptom association probability. However, it should be noted that some authors have questioned the clinical accuracy of these indexes, especially in patients with refractory GERD.[54]

Esophageal pH monitoring allows identification of patients with either normal or abnormal distal esophageal acid exposure and determination of the temporal relationship between their symptoms and acid reflux events. The introduction of the wireless pH capsule system (Bravo reflux testing system, Medtronic), a catheter-free approach for ambulatory esophageal pH monitoring, raised hopes of improved tolerability of the pH test. Surprisingly, patients with functional heartburn were more likely to report retrosternal discomfort after placement of the wireless pH capsule.[55] However, the wireless pH capsule allows 96 hours of pH measurement and, thus, is more sensitive than 24-hour pH monitoring in detecting a positive association between symptoms and

reflux events.[56] As a result, the wireless pH capsule is currently the preferred diagnostic approach for esophageal acid exposure assessment in heartburn patients off PPI treatment.

pH-impedance monitoring provides assessment of nonacidic reflux in addition to acidic reflux. Although the technique has been recommended for the assessment of heartburn patients while they are on PPI treatment, some research has suggested that pH-impedance monitoring off therapy can reduce the number of functional heartburn patients.[13] Adding patients with abnormal weakly acidic reflux to those with abnormal acidic reflux increases the number of patients diagnosed with GERD and, thus, reduces the number of patients diagnosed with functional heartburn. Furthermore, because they reflect the integrity of the esophageal mucosa, impedance baseline measurements have been suggested to help determine whether heartburn patients have GERD or functional heartburn.[57-59] GERD patients have lower impedance baseline levels as compared with healthy controls and functional heartburn patients. A mucosal impedance catheter was recently introduced to measure electrical mucosal impedance of the esophageal lining by direct mucosal contact during upper endoscopy. This technique utilizes a probe that includes two 2-mm–long impedance sensing electrodes positioned 1 mm from the tip of a 2-mm soft catheter. Recent publications have demonstrated the capability of mucosal impedance to identify functional heartburn patients by showing that these heartburn patients have esophageal mucosal impedance values that are different from normal controls.[60,61]

All patients with normal reflux testing, regardless of whether their symptom indexes are positive, should undergo esophageal manometry to exclude a major esophageal motor disorder. Only after negative esophageal manometry can the diagnosis of functional heartburn be established.

Figure 3 shows a diagnostic algorithm of functional heartburn in refractory heartburn patients who failed twice-daily PPIs.[11]

Treatment

Because of the evolution of the definition of functional heartburn from Rome II to Rome IV, the literature provides mixed information regarding response to PPI treatment in patients with functional heartburn.[62] Research using the Rome II definition of functional heartburn (with the reflux hypersensitivity group included) has shown that approximately 50% of patients with functional heartburn responded to treatment with standard-dose PPIs.[63] Several studies of patients with functional heartburn (using the Rome II definition) have

demonstrated that a double or even triple dose of PPIs is needed to improve symptom response (37%-60%).[64-66] However, it is likely that the reflux hypersensitivity group is responsible for the partial response to PPIs of the Rome II–defined functional heartburn group.

Rome III removed the reflux hypersensitivity group from the definition of functional heartburn, making it highly unlikely that the newly defined functional heartburn patients will respond to PPI treatment. Interestingly, a small subset of patients (up to 25%) that falls under the category of functional heartburn per Rome III responds to PPI treatment.[67] The reason for this response is unclear and may not even be durable (placebo effect).

Pain modulators are currently considered to be the mainstay treatment of patients with functional heartburn. Tricyclic antidepressants (TCAs), trazodone, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) have shown some level of efficacy in other functional esophageal disorders, including noncardiac chest pain (NCCP).[68,69] Although the use of antidepressants is highly attractive, research demonstrating their efficacy in functional heartburn patients is scarce. In a recent study, patients with reflux hypersensitivity and functional heartburn were randomized to a fixed dose of 25 mg of imipramine once daily vs placebo.[70] The authors failed to demonstrate the superiority of imipramine over placebo in improving the patients' heartburn symptoms. In general, TCAs should not be given in a fixed dose, and the dose should be carefully titrated in each patient based on symptomatic response.

Psychological interventions are also considered in functional heartburn patients. In a prospective study, the authors demonstrated that biofeedback was effective in NCCP but not in functional heartburn.[71] In contrast, hypnotherapy has been established as a preferred intervention for functional heartburn.[72] In a study, the authors demonstrated that there were consistent and significant changes in heartburn symptoms, esophageal hypervigilance, quality of life, and a trend for improvement in catastrophizing for functional heartburn patients who enrolled in a 7-week session of esophageal-directed hypnotherapy protocol.[72]

Histamine-2 receptor antagonists have been shown to modulate esophageal acid sensitivity in patients with functional heartburn.[73] Tegaserod, a partial 5-hydroxytryptamine-4 agonist, has been shown to improve both chemo- and mechanoreceptor sensitivity to acid perfusion and balloon distention, respectively.[74] Additionally, 2 weeks of tegaserod 6 mg twice daily markedly improved patients' heartburn and other upper GI tract–related symptoms compared with placebo.

In a randomized, placebo-controlled pilot study, patients with functional heartburn were treated with
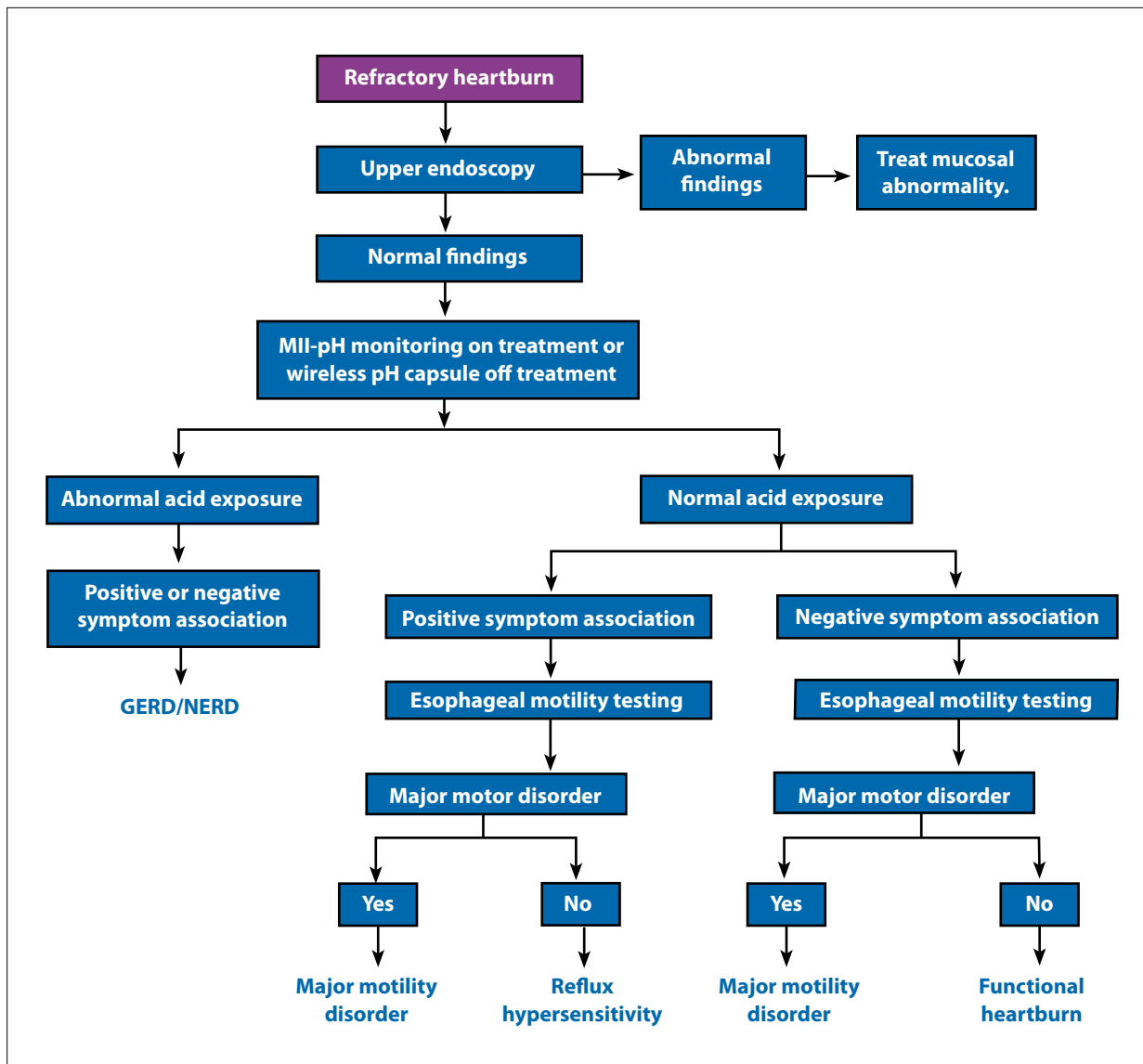
Figure 3. Diagnostic algorithm of functional heartburn in refractory heartburn patients who failed twice-daily proton pump inhibitor therapy.

GERD, gastroesophageal reflux disease; MII, multichannel intraluminal impedance; NERD, nonerosive reflux disease.

Adapted from Yamasaki T, Fass R.[11]

omeprazole 20 mg before breakfast and randomized to receive either melatonin 6 mg, nortriptyline 25 mg, or placebo at bedtime. At the end of the follow-up period, which lasted 3 months, melatonin improved GERD–Health-Related Quality-of-Life scores compared with nortriptyline (P=.0015) and placebo (P<.0001).[75] This study suggested that melatonin was a safe and effective treatment for functional heartburn.

Antireflux surgery should be avoided in patients with functional heartburn, as normal preoperative acid exposure is a risk factor for poor outcome of fundoplication.[76,77]

Summary

Functional heartburn, as defined by Rome IV criteria, is the presence of typical heartburn symptoms in patients with normal upper endoscopy findings, normal esophageal pH testing, and a negative correlation between symptoms and reflux events. The disorder is

very common, affecting 21% to 24% of all nontreated heartburn patients. Functional heartburn overlaps with other functional GI disorders and is often accompanied by psychological comorbidities. As with all functional esophageal disorders, the main underlying mechanism is esophageal hypersensitivity. A negative upper endoscopy with esophageal biopsies, pH-impedance monitoring or wireless pH capsule, and high-resolution esophageal manometry are needed to diagnose the disorder. Functional heartburn is the most common underlying cause for refractory heartburn, affecting 5% of patients. Both functional heartburn and reflux hypersensitivity account for more than 90% of all refractory heartburn patients. The cornerstone of therapy is neuromodulators, including TCAs, SSRIs, and SNRIs. Psychological intervention is paramount for successful treatment in patients with psychological comorbidity. Complementary and alternative medicine may have a therapeutic role in these patients.

The authors have no relevant conflicts of interest to disclose.

References

1. Drossman DA, Corazziari R, Talley NJ, et al, eds. *Rome II: The Functional Gastrointestinal Disorders. Diagnosis, Pathophysiology and Treatment: A Multinational Consensus.* 2nd ed. McLean, VA: Degnon Associates; 2000.

2. Drossman DA, ed. *Rome III: The Functional Gastrointestinal Disorders.* 3rd ed. McLean, VA: Degnon Associates; 2006.

3. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? *Aliment Pharmacol Ther.* 2005;22(2):79-94.

4. Fass R, Naliboff B, Higa L, et al. Differential effect of long-term esophageal acid exposure on mechanosensitivity and chemosensitivity in humans. *Gastroenterology.* 1998;115(6):1363-1373.

5. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology.* 2016;150(6):1262-1279.e2.

6. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Esophageal disorders. *Gastroenterology.* 2016;150(6):1368-1379.

7. Winters C Jr, Spurling TJ, Chobanian SJ, et al. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology.* 1987;92(1):118-124.

8. Johansson KE, Ask P, Boeryd B, Fransson SG, Tibbling L. Oesophagitis, signs of reflux, and gastric acid secretion in patients with symptoms of gastro-oesophageal reflux disease. *Scand J Gastroenterol.* 1986;21(7):837-847.

9. Fass R, Fennerty MB, Vakil N. Nonerosive reflux disease—current concepts and dilemmas. *Am J Gastroenterol.* 2001;96(2):303-314.

10. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. *J Clin Gastroenterol.* 2007;41(2):131-137.

11. Yamasaki T, Fass R. Reflux hypersensitivity: a new functional esophageal disorder. *J Neurogastroenterol Motil.* 2017;23(4):495-503.

12. 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(2):159-168.

13. 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(7):542-547.

14. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut.* 2006;55(10):1398-1402.

15. Roman S, Keefer L, Imam H, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. *Neurogastroenterol Motil.* 2015;27(11):1667-1674.

16. Shapiro M, Green C, Bautista JM, et al. Functional heartburn patients demonstrate traits of functional bowel disorder but lack a uniform increase of chemoreceptor sensitivity to acid. *Am J Gastroenterol.* 2006;101(5):1084-1091.

17. 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(9):1185-1191.

18. de Bortoli N, Frazzoni L, Savarino EV, et al. Functional heartburn overlaps with irritable bowel syndrome more often than GERD. *Am J Gastroenterol.* 2016;111(12):1711-1717.

19. Hershcovici T, Fass R. GERD: are functional heartburn and functional dyspepsia one disorder? *Nat Rev Gastroenterol Hepatol.* 2010;7(2):71-72.

20. de Bortoli N, Martinucci I, Bellini M, et al. Overlap of functional heartburn and gastroesophageal reflux disease with irritable bowel syndrome. *World J Gastroenterol.* 2013;19(35):5787-5797.

21. Hershcovici T, Zimmerman J. Functional heartburn vs. non-erosive reflux disease: similarities and differences. *Aliment Pharmacol Ther.* 2008;27(11):1103-1109.

22. Bilgi MM, Vardar R, Yildirim E, Veznedaroğlu B, Bor S. Prevalence of psychiatric comorbidity in symptomatic gastroesophageal reflux subgroups. *Dig Dis Sci.* 2017;62(4):984-993.

23. Jang SH, Ryu HS, Choi SC, Lee SY. Psychological factors influence the overlap syndrome in functional gastrointestinal disorders and their effect on quality of life among firefighters in South Korea. *J Dig Dis.* 2016;17(4):236-243.

24. Surdea Blaga T, Dumitrascu D, Galmiche JP, Bruley des Varannes S. Functional heartburn: clinical characteristics and outcome. *Eur J Gastroenterol Hepatol.* 2013;25(3):282-290.

25. Fass R, Tougas G. Functional heartburn: the stimulus, the pain, and the brain. *Gut.* 2002;51(6):885-892.

26. Yang M, Li ZS, Chen DF, et al. Quantitative assessment and characterization of visceral hyperalgesia evoked by esophageal balloon distention and acid perfusion in patients with functional heartburn, nonerosive reflux disease, and erosive esophagitis. *Clin J Pain.* 2010;26(4):326-331.

27. Yang M, Li Z-S, Xu X-R, et al. Characterization of cortical potentials evoked by oesophageal balloon distention and acid perfusion in patients with functional heartburn. *Neurogastroenterol Motil.* 2006;18(4):292-299.

28. Hobson AR, Furlong PL, Aziz Q. Oesophageal afferent pathway sensitivity in non-erosive reflux disease. *Neurogastroenterol Motil.* 2008;20(8):877-883.

29. Rodriguez-Stanley S, Robinson M, Earnest DL, Greenwood-Van Meerveld B, Miner PB Jr. Esophageal hypersensitivity may be a major cause of heartburn. *Am J Gastroenterol.* 1999;94(3):628-631.

30. Thoua NM, Khoo D, Kalantzis C, Emmanuel AV. Acid-related oesophageal sensitivity, not dysmotility, differentiates subgroups of patients with non-erosive reflux disease. *Aliment Pharmacol Ther.* 2008;27(5):396-403.

31. Weijenborg PW, Smout AJ, Bredenoord AJ. Esophageal acid sensitivity and mucosal integrity in patients with functional heartburn. *Neurogastroenterol Motil.* 2016;28(11):1649-1654.

32. Kondo T, Miwa H. The role of esophageal hypersensitivity in functional heartburn. *J Clin Gastroenterol.* 2017;51(7):571-578.

33. Siddiqui A, Rodriguez-Stanley S, Zubaidi S, Miner PB Jr. Esophageal visceral sensitivity to bile salts in patients with functional heartburn and in healthy control subjects. *Dig Dis Sci.* 2005;50(1):81-85.

34. Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. *Gut.* 1995;37(1):7-12.

35. Frazzoni M, De Micheli E, Zentilin P, Savarino V. Pathophysiological characteristics of patients with non-erosive reflux disease differ from those of patients with functional heartburn. *Aliment Pharmacol Ther.* 2004;20(1):81-88.

36. Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. Non-erosive reflux disease (NERD)—acid reflux and symptom patterns. *Aliment Pharmacol Ther.* 2003;17(4):537-545.

37. Cicala M, Emerenziani S, Caviglia R, et al. Intra-oesophageal distribution and perception of acid reflux in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther.* 2003;18(6):605-613.

38. Chu C, Du Q, Li C, et al. Ambulatory 24-hour multichannel intraluminal impedance-pH monitoring and high resolution endoscopy distinguish patients with non-erosive reflux disease from those with functional heartburn. *PLoS One.* 2017;12(4):e0175263.

39. Schey R, Shapiro M, Navarro-Rodriguez T, et al. Comparison of the different characteristics of sensed reflux events among different heartburn groups. *J Clin Gastroenterol.* 2009;43(8):699-704.

40. Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Characteristics of gastro-esophageal reflux in symptomatic patients with and without excessive esophageal acid exposure. *Am J Gastroenterol*. 2006;101(11):2470-2475.

41. Caviglia R, Ribolsi M, Maggiano N, et al. Dilated intercellular spaces of esoph-ageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. *Am J Gastroenterol*. 2005;100(3):543-548.

42. Emerenziani S, Sifrim D, Habib FI, et al. Presence of gas in the refluxate enhances reflux perception in non-erosive patients with physiological acid expo-sure of the oesophagus. *Gut*. 2008;57(4):443-447.

43. Martinucci I, de Bortoli N, Savarino E, et al. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. *Neurogastroenterol Motil*. 2014;26(4):546-555.

44. Liu L, Ergun G, Ertan A, Woods K, Sachs I, Younes M. Detection of oxida-tive DNA damage in oesophageal biopsies of patients with reflux symptoms and normal pH monitoring. *Aliment Pharmacol Ther*. 2003;18(7):693-698.

45. Lind T, Havelund T, Lundell L, et al. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis—a placebo-controlled randomized trial. *Aliment Pharmacol Ther*. 1999;13(7):907-914.

46. Park EY, Choi MG, Baeg M, et al. The value of early wireless esophageal pH monitoring in diagnosing functional heartburn in refractory gastroesophageal reflux disease. *Dig Dis Sci*. 2013;58(10):2933-2939.

47. Fass R. Functional heartburn: what it is and how to treat it. *Gastrointest Endosc Clin N Am*. 2009;19(1):23-33, v.

48. Luo X, Guo XX, Wang WF, Peng LH, Yang YS, Uedo N. Autofluorescence imaging endoscopy can distinguish non-erosive reflux disease from functional heartburn: a pilot study. *World J Gastroenterol*. 2016;22(14):3845-3851.

49. Fock KM, Teo EK, Ang TL, Tan JY, Law NM. The utility of narrow band imaging in improving the endoscopic diagnosis of gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2009;7(1):54-59.

50. Schindlbeck NE, Wiebecke B, Klauser AG, Voderholzer WA, Müller-Lissner SA. Diagnostic value of histology in non-erosive gastro-oesophageal reflux disease. *Gut*. 1996;39(2):151-154.

51. Savarino E, Zentilin P, Mastracci L, et al. Microscopic esophagitis distinguishes patients with non-erosive reflux disease from those with functional heartburn. *J Gastroenterol*. 2013;48(4):473-482.

52. Vela MF, Craft BM, Sharma N, Freeman J, Hazen-Martin D. Refractory heartburn: comparison of intercellular space diameter in documented GERD vs. functional heartburn. *Am J Gastroenterol*. 2011;106(5):844-850.

53. Kandulski A, Jechorek D, Caro C, et al. Histomorphological differentiation of non-erosive reflux disease and functional heartburn in patients with PPI-refractory heartburn. *Aliment Pharmacol Ther*. 2013;38(6):643-651.

54. 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(10):868-874.

55. Lee Y-C, Wang H-P, Chiu H-M, et al. Patients with functional heartburn are more likely to report retrosternal discomfort during wireless pH monitoring. *Gastrointest Endosc*. 2005;62(6):834-841.

56. Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D. Inconsis-tency 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(2):265-272.

57. Farré R, Blondeau K, Clement D, et al. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. *Gut*. 2011;60(7):885-892.

58. Kandulski A, Weigt J, Caro C, Jechorek D, Wex T, Malfertheiner P. Esopha-geal intraluminal baseline impedance differentiates gastroesophageal reflux disease from functional heartburn. *Clin Gastroenterol Hepatol*. 2015;13(6):1075-1081.

59. Woodland P, Al-Zinaty M, Yazaki E, Sifrim D. In vivo evaluation of acid-induced changes in oesophageal mucosa integrity and sensitivity in non-erosive reflux disease. *Gut*. 2013;62(9):1256-1261.

60. Ates F, Yuksel ES, Higginbotham T, et al. Mucosal impedance discriminates GERD from non-GERD conditions. *Gastroenterology*. 2015;148(2):334-343.

61. Fass R. Esophageal mucosal impedance: is it time to forgo prolonged gastro-esophageal reflux recordings? *Gastroenterology*. 2015;148(2):282-285.

62. Dickman R, Fass R. Functional heartburn. *Curr Treat Options Gastroenterol*. 2005;8(4):285-291.

63. Lind T, Havelund T, Carlsson R, et al. Heartburn without oesophagitis: effi-cacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol*. 1997;32(10):974-979.

64. Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, et al. Omeprazole as a diagnos-tic tool in gastroesophageal reflux disease. *Am J Gastroenterol*. 1997;92(11):1997-2000.

65. Fass R, Ofman JJ, Gralnek IM, et al. Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastroesophageal reflux disease. *Arch Intern Med*. 1999;159(18):2161-2168.

66. Watson RG, Tham TC, Johnston BT, McDougall NI. 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 oesophagus." *Gut*. 1997;40(5):587-590.

67. Zerbib F, Belhocine K, Simon M, et al. Clinical, but not oesophageal pH-impedance, profiles predict response to proton pump inhibitors in gastro-oesoph-ageal reflux disease. *Gut*. 2012;61(4):501-506.

68. Clouse RE, Lustman PJ, Eckert TC, Ferney DM, Griffith LS. Low-dose tra-zodone for symptomatic patients with esophageal contraction abnormalities. A double-blind, placebo-controlled trial. *Gastroenterology*. 1987;92(4):1027-1036.

69. Cannon RO III, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med*. 1994;330(20):1411-1417.

70. Limsrivilai J, Charatcharoenwitthaya P, Pausawasdi N, Leelakusolvong S. Imipramine for treatment of esophageal hypersensitivity and functional heartburn: a randomized placebo-controlled trial. *Am J Gastroenterol*. 2016;111(2):217-224.

71. Shapiro M, Shanani R, Taback H, Abramowich D, Scapa E, Broide E. Func-tional chest pain responds to biofeedback treatment but functional heartburn does not: what is the difference? *Eur J Gastroenterol Hepatol*. 2012;24(6):708-714.

72. Riehl ME, Pandolfino JE, Palsson OS, Keefer L. Feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn. *Dis Esophagus*. 2016;29(5):490-496.

73. Rodriguez-Stanley S, Ciociola AA, Zubaidi S, Proskin HM, Miner PB Jr. A single dose of ranitidine 150 mg modulates oesophageal acid sensitivity in patients with functional heartburn. *Aliment Pharmacol Ther*. 2004;20(9):975-982.

74. Rodriguez-Stanley S, Zubaidi S, Proskin HM, Kralstein JR, Shetzline MA, Miner PB Jr. Effect of tegaserod on esophageal pain threshold, regurgitation, and symptom relief in patients with functional heartburn and mechanical sensitivity. *Clin Gastroenterol Hepatol*. 2006;4(4):442-450.

75. Basu PP, Hempole H, Krishnaswamy N, et al. The effect of melatonin in functional heartburn: a randomized, placebo-controlled clinical trial. *OJGas*. 2014;4(2):56-61.

76. Khajanchee YS, Hong D, Hansen PD, Swanström LL. Outcomes of antireflux surgery in patients with normal preoperative 24-hour pH test results. *Am J Surg*. 2004;187(5):599-603.

77. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg*. 1999;3(3):292-300.