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
Rome III also suggested that patients with heartburn and normal endoscopy findings should be divided into patients with NERD and patients with functional heartburn. 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).

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.

**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. 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

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**Figure 1.** Classification of patients with normal endoscopy findings and no history of documented gastroesophageal reflux disease (GERD) using Rome IV criteria.
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, absent contractility), or structural abnormality. 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. 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. However, later studies that were performed in the community setting revealed that up to 70% of these patients have normal endoscopy findings. 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. 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. Thus, functional heartburn accounts for 21% of all untreated patients presenting with heartburn (Figure 2). One study assessed 329 endoscopy-negative patients with pH-impedance monitoring off PPI treatment. 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. In patients with refractory heartburn who failed twice-daily PPIs, the prevalence of functional heartburn can reach 52% to 54%. 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.

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). 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

<table>
<thead>
<tr>
<th>Table 2. Diagnostic Criteria for Functional Heartburn (Rome IV)</th>
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<td><strong>Must include all of the following:</strong></td>
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<tr>
<td>• Burning retrosternal discomfort or pain</td>
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<tr>
<td>• No symptom relief despite optimal antisecretory therapy</td>
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<tr>
<td>• 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</td>
</tr>
<tr>
<td>• Absence of major esophageal motor disorder (achalasia, esophagogastric junction outflow obstruction, distal esophageal spasm, jackhammer esophagus, absent contractility)</td>
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*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.*
chest pain, functional dyspepsia, and irritable bowel syndrome (IBS), are relatively common in both disorders.\textsuperscript{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.\textsuperscript{17} Several studies have emphasized that IBS symptoms are strong predictors of heartburn severity in patients with functional heartburn.\textsuperscript{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.\textsuperscript{16} However, a study claimed that major depressive disorders were significantly more common in functional heartburn patients as compared with NERD patients.\textsuperscript{22} A recent study suggested that psychological factors may drive the overlap between functional GI disorders, such as functional heartburn with functional dysphagia.\textsuperscript{21}

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.\textsuperscript{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.\textsuperscript{25-27} Furthermore, objective neurophysiologic measures of esophageal-evoked potential latency revealed that functional heartburn patients achieve equivalent esophageal sensitivity.\textsuperscript{28} By contrast, stimulus response functions to acid perfusion in patients with functional heartburn gave mixed results. Rodriguez-Stanley and colleagues\textsuperscript{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\textsuperscript{26} reported that

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**Figure 2.** Percentage of functional heartburn patients among patients with normal endoscopy findings.

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patients with functional heartburn are more sensitive to mechanical and chemical stimuli than NERD patients. Thoua and colleagues\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{32}

Central neural mechanisms,\textsuperscript{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\textsuperscript{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.\textsuperscript{27} Frazzoni and colleagues\textsuperscript{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\textsuperscript{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 10.9%; \(P=0.0001\)). 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.\textsuperscript{36}

Several local factors have been suggested to play an important role in symptom generation of patients with functional heartburn. Cicala and colleagues\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{41} However, using Rome II criteria, these studies\textsuperscript{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.\textsuperscript{3} 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.\textsuperscript{40,42} However, the presence of gas in the refluxate appears to enhance reflux perception in functional heartburn patients\textsuperscript{42} and those with reflux hypersensitivity. Baseline impedance levels were found to be similar when functional heartburn patients were compared with healthy controls.\textsuperscript{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.\textsuperscript{44} It is yet to be determined whether these are primarily reflux hypersensitivity patients.

Shapiro and colleagues\textsuperscript{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.
**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. 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, irritable bowel syndrome. Concomitant functional gastrointestinal disorder (functional chest pain, functional dyspepsia, irritable bowel syndrome) may overlap with GERD. Esophageal dysmotility is rare, hiatal hernia is uncommon, and health-related quality of life is similar to that of other GERD phenotypes. Psychological comorbidity (depression, anxiety, somatization) is also not uncommon.

Table 3. Clinical Characteristics of Patients With Functional Heartburn

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
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<tr>
<td>More common</td>
<td>in women than in men</td>
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<tr>
<td>Middle age</td>
<td></td>
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<tr>
<td>Long history</td>
<td>of heartburn</td>
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<tr>
<td>Symptom severity and frequency</td>
<td>similar to those of GERD phenotypes</td>
</tr>
<tr>
<td>Concomitant functional gastrointestinal disorder</td>
<td>(functional chest pain, functional dyspepsia, irritable bowel syndrome)</td>
</tr>
<tr>
<td>May overlap with GERD</td>
<td></td>
</tr>
<tr>
<td>Esophageal dysmotility</td>
<td>rare</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>uncommon</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>similar to that of other GERD phenotypes</td>
</tr>
<tr>
<td>Psychological comorbidity</td>
<td>(depression, anxiety, somatization)</td>
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GERD, gastroesophageal reflux disease.

**Diagnosis**

Establishing the diagnosis of functional heartburn requires 2 invasive procedures: upper endoscopy and reflux monitoring. 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. 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. 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. For example, the presence of a normal diameter of intercellular spaces in the context of heartburn symptoms suggests functional heartburn. 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.

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.

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. 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.
reflux events. 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. Adding patients with abnormal weakly acidic reflux to those with abnormal acidic reflux increases 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. 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 sensors 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.

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.

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. 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. 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%). 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. 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). 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 versus placebo. 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. In contrast, hypnotherapy has been established as a preferred intervention for functional heartburn. 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.

Histamine-2 receptor antagonists have been shown to modulate esophageal acid sensitivity in patients with functional heartburn. Tegaserod, a partial 5-hydroxytryptamine-4 agonist, has been shown to improve both chemo- and mechanoreceptor sensitivity to acid perfusion and balloon distention, respectively. 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...
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). 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


