

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

Section Editor: Joel E. Richter, MD

## Functional Heartburn



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### **G&H** How does functional heartburn differ from heartburn caused by gastroesophageal reflux disease?

**RF** Functional heartburn is defined as the presence of the same heartburn symptoms that are caused by gastroesophageal reflux disease but without any evidence of abnormal esophageal acid exposure, physiologic acid reflux exposure that highly correlates with symptoms and recognized esophageal motility disorders. Thus, functional heartburn is not caused by gastroesophageal reflux disease or a well-defined esophageal motility disorder.

### **G&H** What is the cause of functional heartburn then?

**RF** The mechanisms responsible for functional heartburn remain poorly understood, and it is not yet clear why this condition develops in some patients and not in others. What we do know is that esophageal symptoms are not stimulus-specific (ie, symptoms such as heartburn may be caused by different intraluminal stimuli). For example, heartburn can be caused by a chemical stimulus such as reflux, or it can be caused by a mechanical stimulus such as esophageal distension. Esophageal hypersensitivity has been suggested to play an important role in these patients. (Patients demonstrate lower thresholds for pain perception, causing them to respond with heartburn as the main symptom to even physiologic or mildly pathologic esophageal events.) Another possible cause of functional heartburn

could be altered central processing of peripheral stimuli. A variety of central factors, such as sleep deprivation, stress, anxiety, and other psychological disorders, may also play a role in these patients. Because we do not know the exact underlying cause of functional heartburn, this condition falls under the category of functional esophageal disorders, of which there are currently 4 (functional chest pain, functional heartburn, functional dysphagia, and globus).

### **G&H** Is there any overlap between patients who have functional heartburn and patients who have gastroesophageal reflux disease or any other gastrointestinal disorders?

**RF** Some patients may have gastroesophageal reflux disease and a component of esophageal hypersensitivity, but this is not actually functional heartburn; by definition, it is not possible to have gastroesophageal reflux disease with functional heartburn. Likewise, there is no evidence that, over time, patients with functional heartburn develop erosive esophagitis, Barrett esophagus, or esophageal cancer because functional heartburn is not caused by reflux.

However, as with other functional esophageal disorders, there is some evidence that functional heartburn may overlap with other functional gastrointestinal disorders, such as functional dyspepsia, noncardiac chest pain, and irritable bowel syndrome. The high degree of overlap among the different functional bowel disorders has raised the hypothesis that these patients have a disorder that involves all levels of the gastrointestinal tract.

### G&H What tests can be used to establish a diagnosis of functional heartburn?

**RF** Currently, functional heartburn is still a diagnosis of exclusion. Patients have to have a normal upper endoscopy, a pH test or impedance-plus-pH test that is normal, and the absence of any evidence of a correlation between physiologic reflux events, either weakly acidic or acidic, and heartburn symptoms. Patients with functional heartburn have esophageal acid exposure within the physiologic range, but there should be no evidence that their heartburn symptoms are related to these normal physiologic reflux events. Nowadays, some physicians also require a normal histology on esophageal mucosal biopsies to establish a diagnosis of functional heartburn.

Some physicians also believe that these patients should demonstrate a complete lack of response—not just a partial response—to proton pump inhibitor therapy. In fact, it has been suggested by some that a lack of response to proton pump inhibitor therapy should be used as the main criterion to diagnose functional heartburn, as studies have shown that heartburn patients treated with twice-daily proton pump inhibitor therapy who demonstrate complete lack of response have a greater-than-90% chance of having functional heartburn. However, this criterion is not an absolute indicator of functional heartburn; the only absolute indicator is the systematic diagnostic testing mentioned above.

### G&H What should be the first line of treatment for functional heartburn?

**RF** Once a diagnosis of functional heartburn is made, treatment should be based on pain modulation in order to find ways to alter pain perception. The pain modulators typically used for treatment of functional heartburn include different types of antidepressants, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and trazodone. There is also some evidence that 5-hydroxytryptamine (5-HT)<sub>3</sub> antagonists and 5-HT<sub>4</sub> agonists can be used for the treatment of functional heartburn.

Some physicians have tried using other therapeutic options, for example medications such as sucralfate (Carafate, Aptalis) or aluminum hydroxide and magnesium trisilicate (Gaviscon, Sanofi Aventis) in the hopes of improving mucosal protection. Psychological intervention (such as cognitive behavioral therapy, muscle relaxation techniques, and even hypnotherapy) and alternative medicine techniques (such as acupuncture) have also been tried in this patient population. However, at the end of the day, it is pain modulation that plays the most important role in treatment of patients with functional heartburn.

### G&H According to studies, how effective are these therapies?

**RF** Unfortunately, very few studies have examined the efficacy of the various therapeutic options currently available for patients with functional heartburn, although the few studies conducted thus far have been positive. One study showed that fluoxetine, an SSRI, can improve symptoms in these patients more than omeprazole after 6 weeks of treatment. Another study showed that tegaserod, a 5-HT<sub>4</sub> agonist, was able to improve symptoms such as heartburn, regurgitation, early fullness, and bloating in patients with functional heartburn.

There have not yet been any studies examining the use of sucralfate or aluminum hydroxide and magnesium trisilicate in this patient population, and limited data are available for psychological intervention and alternative medicine techniques. One study demonstrated that acupuncture markedly improved heartburn symptoms in patients who failed proton pump inhibitor treatment and had normal esophageal function tests.

### G&H Since there are not much data on these treatment options, how does a physician decide which medication to give to a particular patient?

**RF** The decision is most likely based on the doctor's experience and comfort with pain modulators. In addition, older patients, particularly older men, may be more susceptible to adverse effects. Thus, medications such as tricyclic antidepressants should be given in low, non-mood-altering doses. Some physicians base their treatment decisions mainly on the current available data, which means administering SSRIs and 5-HT<sub>4</sub> agonists, as these agents have undergone the most studies to date (although the studies have been few in number).

### G&H What are the ideal doses for these agents?

**RF** The ideal dose depends on the type of medication. In the case of tricyclic antidepressants, usually the physician starts with a very low dose, 5 to 10 mg, at bedtime and then increases the dosage by 10-mg increments to a goal of 30 to 50 mg. However, some physicians believe that patients with functional heartburn may need less than 30 to 50 mg.

The ideal doses of SSRIs and SNRIs are different. Many times, it depends on the chosen medication. In the case of venlafaxine, 75 mg at bedtime is commonly used.

However, when prescribing these medications, physicians should keep in mind that adverse effects are not uncommon, especially with tricyclic antidepressants. Common adverse effects include constipation, difficulty to urinate, blurred vision, dry mouth, sexual dysfunc-

tion, and drowsiness with tricyclic antidepressants and nausea, insomnia, dizziness, sexual dysfunction, and drowsiness with SSRIs.

### G&H Are there any surgical interventions?

**RF** Presently, surgery is not an option. Surgeons often prefer not to operate on patients with functional heartburn because they consider these patients to have some type of pain syndrome. In fact, the idea that functional heartburn is a psychiatric problem, and not a real disease, has been shared by many physicians for many years. One of the most important advances that we have made recently in esophageal disorders has been the understanding and acceptance of these patients. Before, we thought that only acid could trigger heartburn; now, we understand that heartburn can be caused by other underlying mechanisms.

### G&H Do patients with functional heartburn require lifelong treatment?

**RF** It appears that most of these patients require lifelong treatment and will probably be seen by physicians on a regular, long-term basis. Some may require a more comprehensive therapeutic approach that includes psychologists and social workers in addition to a gastroenterologist. In some functional esophageal disorders, there is evidence of decreased prevalence of the disease as patients age. This could also be true for patients with functional heartburn, but, as of yet, there is very little evidence of this possibility in this patient population.

### G&H Will there ever be a cure for functional heartburn?

**RF** Over time, I think that we will better understand the underlying mechanisms of symptoms in this patient

population and, accordingly, will be able to establish better therapeutic modalities. What is coming between us and a cure is the fact that we either do not have the proper tools to identify the exact pathophysiologic mechanisms in these patients or, at this point, have any treatment that could cure these patients. So I believe that it is just a matter of time before we find a cure for this condition.

### G&H What are the next steps in this area?

**RF** There are several ongoing studies looking at various therapeutic modalities, mostly different types of antidepressants, in these patients. One of the future directions is to try and develop novel pain modulators that are specific to the esophagus and, thus, can better treat functional heartburn.

Future testing in this area should also focus on trying to better understand the underlying mechanisms of functional heartburn as well as its prevalence, demographics, and natural course. All of these factors will help us better characterize the disease and, accordingly, better understand it and enable us to develop proper therapy for these patients. Currently, therapeutic trials in this area are rare, and even simple physiologic studies are relatively scarce.

*Dr Fass has no relevant conflicts of interest to disclose.*

### Suggested Reading

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