

Journal Pre-proof

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Ronnie Fass, Frank Zerbib, C. Prakash Gyawali



PII: S0016-5085(20)30128-1
DOI: <https://doi.org/10.1053/j.gastro.2020.01.034>
Reference: YGAST 63176

To appear in: *Gastroenterology*
Accepted Date: 23 January 2020

Please cite this article as: Fass R, Zerbib F, Gyawali CP, AGA Clinical Practice Update on Functional Heartburn: Expert Review, *Gastroenterology* (2020), doi: <https://doi.org/10.1053/j.gastro.2020.01.034>.

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1-14-2020

AGA Clinical Practice Update on Functional Heartburn: Expert Review

Ronnie Fass¹
Frank Zerbib²,
C. Prakash Gyawali³

¹ Digestive Health Center, MetroHealth System, Cleveland, USA

²Department of Gastroenterology, Bordeaux University Hospital, and Université de Bordeaux, Bordeaux, France

³Division of Gastroenterology, Washington University School of Medicine, St. Louis, USA

Short title: Functional heartburn

Best Practice Advice word count: 283 words; Manuscript word count: 3157 words

Address all correspondence to:

C. Prakash Gyawali, MD
Professor of Medicine
Division of Gastroenterology
660 South Euclid Ave., Campus Box 8124
Saint Louis, MO 63110
Phone: 314-454-8201
Fax: 314-454-5107
Email: cprakash@dom.wustl.edu

Competing Interests: No conflicts of interest exist. There was no funding for this study.

Disclosures: RF: Ironwood, Takeda, Chinoin (consulting), Astrazeneca, Takeda, Horizon, Diversitek, Eisai Pharmaceuticals (speaking); Ironwood, Salix (research)

FZ: Reckitt Benckiser (consulting)

CPG: Medtronic, Diversatek (teaching and consulting), Ironwood, Quintiles (consulting)

Author roles: All authors contributed equally to the manuscript.

Acknowledgments: This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of Clinical Gastroenterology and Hepatology

BEST PRACTICE ADVICE

1. A diagnosis of functional heartburn should be considered when retrosternal burning pain or discomfort persists despite maximal (double dose) PPI therapy taken appropriately before meals over a 3-month period
2. A diagnosis of functional heartburn requires upper endoscopy with esophageal biopsies to rule out anatomic and mucosal abnormalities, esophageal high resolution manometry to rule out major motor disorders, and pH monitoring off PPI therapy (or pH-impedance monitoring on therapy in patients with proven GERD) to document physiologic levels of esophageal acid exposure in the distal esophagus with absence of reflux-symptom association (i.e. negative symptom index and symptom association probability)
3. Overlap of functional heartburn with proven GERD is diagnosed according to Rome IV criteria when heartburn persists despite maximal PPI therapy in patients with history of proven GERD (positive pH study, erosive esophagitis, Barrett's esophagus, or esophageal ulcer), and pH impedance testing on PPI therapy demonstrates physiologic acid exposure without reflux-symptom association (i.e. negative symptom index and symptom association probability).
4. Proton pump inhibitors have no therapeutic value in functional heartburn, the exception being proven GERD that overlaps with functional heartburn
5. Neuromodulators, including tricyclic antidepressants, selective serotonin reuptake inhibitors, tegaserod and histamine-2 receptor antagonists have benefit as either primary therapy in functional heartburn or as add-on therapy in functional heartburn that overlaps with proven GERD

6. Based on available evidence, acupuncture and hypnotherapy may have benefit as monotherapy in functional heartburn, or as adjunctive therapy combined with other therapeutic modalities.
7. Based on available evidence, anti-reflux surgery and endoscopic GERD treatment modalities have no therapeutic benefit in functional heartburn and should not be recommended.

INTRODUCTION

Functional heartburn consists of retrosternal burning similar to that experienced in gastroesophageal reflux disease (GERD), but without evidence of abnormal esophageal acid exposure on ambulatory reflux monitoring, major esophageal motor disorders on high resolution manometry, or esophageal mucosal pathology (such as erosive esophagitis, Barrett's esophagus or eosinophilic esophagitis) on endoscopy with esophageal biopsies¹. In contrast, despite identical clinical presentation, a diagnosis of non-erosive reflux disease (NERD) requires the presence of abnormal esophageal acid exposure on ambulatory reflux monitoring^{1,2}. The prevalence of functional heartburn in the community is difficult to determine, but as many as 21-39% of patients with heartburn refractory to proton pump inhibitor (PPI) undergoing pH-impedance monitoring fulfil criteria for functional heartburn³⁻⁶. Functional heartburn is important to recognize, as without investigation, this condition might be considered equivalent with GERD, and treating physicians could continue acid suppressive therapy unnecessarily or escalate anti-reflux treatments, which might even lead to harm. Importantly, acid suppressive therapies are typically not effective, and antireflux surgery or other invasive antireflux modalities should be avoided. This is primarily because acid does not trigger functional heartburn symptoms, as evident from acid perfusion studies comparing functional heartburn to NERD patients⁷.

There have been advances in esophageal testing to differentiate functional heartburn from refractory reflux disease. Studies of afferent nerves in esophageal mucosa have demonstrated that functional heartburn patients have deep localization of nerves similar to healthy volunteers rather than superficial localization seen in NERD, supporting a nociceptive pathophysiologic mechanism in functional heartburn similar to other functional gastrointestinal disorders⁸. Furthermore, balloon distension studies have demonstrated a similar degree of visceral

hypersensitivity in the esophagus and the rectum in patients with functional heartburn, supporting a generalized increase in perception of visceral stimuli⁹. There is also a high likelihood of anxiety and other affective disorders in patients with functional heartburn¹⁰. These etiological factors indicate that functional heartburn is a separate entity that warrants a multimodal management distinct from GERD patients, since patients with functional heartburn, either alone or overlapping with GERD, will likely not improve unless esophageal perception and underlying affective disorders are adequately managed.

This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of Gastroenterology. This review highlights clinical presentation, modern diagnosis and management of functional heartburn.

CLINICAL PRESENTATION

Many patients with GERD-like symptoms who fail PPI therapy may in fact have a functional disorder, including functional heartburn^{11 5, 12}, diagnosed in as many as a quarter of patients with persistent heartburn on PPI therapy, either by itself or overlapping with established GERD¹³. Heartburn is defined as a burning sensation with pain or discomfort that starts from the epigastrium and radiates retrosternally. While patients may use various terms to describe GERD-like symptoms, including reflux, heartburn, regurgitation, chest pain, chest discomfort, fullness, throat burning, mouth burning, epigastric burning, water brash, belching, sour and bitter taste in the mouth, their association with gastroesophageal reflux needs to be determined by careful

history¹⁴. The clinical presentation of functional heartburn is similar to heartburn due to GERD, but the diagnosis of functional heartburn is commonly considered only in patients with persistent heartburn symptoms, typically without improvement (or even worsening) while on PPI therapy. Diagnostic criteria for NERD, reflux hypersensitivity (heartburn triggered by physiologic reflux episodes) and functional heartburn were redefined by ROME IV¹, leading to stricter diagnostic criteria and less confusion between true GERD/NERD and functional heartburn¹⁵.

Clinical description of heartburn, whether obtained in the office by a primary care provider/gastroenterologist, or from validated symptom questionnaires, has only modest sensitivity and specificity when compared to objective reflux evidence on testing, or to symptom relief with PPI therapy¹⁶⁻¹⁸. Furthermore, the Montreal consensus heartburn-related definitions encompass not just true GERD, but also functional esophageal disorders, both reflux hypersensitivity and functional heartburn, as well as various degrees of overlap between GERD and functional esophageal disorders^{19 20}. This overlap with functional disorders, as well as other non-GERD mechanisms for heartburn, may be partly responsible for the 40% dissatisfaction rate with PPI therapy in patients with heartburn²¹. In a prospective study of 366 patients with refractory heartburn who were enrolled in a Veterans Administration study, 99 (27%) had functional heartburn on the basis of negative esophageal testing including pH-impedance monitoring off acid suppression, while 23 (6%) had non-GERD esophageal disorders, and 7 (2%) had esophageal motility disorders.

The lack of or partial symptom relief despite optimal therapy is an important starting point for consideration of the diagnosis of functional heartburn¹. The impact of heartburn symptoms on quality of life needs to be factored into clinical decision-making and the degree of invasive investigation needed for evaluation and management^{22 23}. The purpose of invasive

investigation is to make a conclusive diagnosis in order to provide precision, personalized management of esophageal symptoms targeted toward the mechanisms of symptom generation^{2, 20}. In functional heartburn, this involves not just initiation of neuromodulators, but potentially, discontinuation of ineffective approaches such as acid suppressive therapy. Thus, functional heartburn should be considered only in patients who report troublesome heartburn symptoms at least 2 times a week for the previous 3 months despite double dose PPI taken appropriately before meals¹. The presence of concurrent functional gastrointestinal disorders and somatization disorder should also be considered²⁴. Indeed, both functional dyspepsia and irritable bowel syndrome are frequently associated with functional heartburn^{10, 25} and negatively impact symptom response to therapies²⁶⁻²⁸.

DIAGNOSIS

Endoscopy is indicated in patients with heartburn who fail an adequate trial of empirical PPI therapy, in order to rule out other esophageal or gastric diseases, including structural abnormalities such as strictures or webs, eosinophilic esophagitis, pill-induced esophagitis, Barrett's esophagus, and neoplasia (Figure 1). The prevalence of erosive esophagitis is less than 10% in patients refractory to PPI therapy^{29 30}; when identified, this indicates poorly controlled persistent acid reflux, or true refractory GERD according to Rome IV¹. Although the prevalence of eosinophilic esophagitis does not exceed 8% in patients presenting with refractory heartburn³⁰⁻³², eosinophilic esophagitis should be ruled out by adequate biopsy sampling to comply with the current definition of functional heartburn.

Since most patients with refractory heartburn unresponsive to PPIs have normal endoscopy and esophageal biopsies, ambulatory reflux monitoring is performed to evaluate for evidence for gastroesophageal reflux (Figure 1). By definition, there should be no link between reflux and symptoms in functional heartburn. According to recent consensus statements^{1,33}, patients without previous evidence of pathological gastroesophageal reflux (i.e. significant peptic esophagitis, Barrett's esophagus, or positive pH study), should be investigated using pH or pH-impedance monitoring off anti-secretory medications to document the level of baseline reflux. High resolution manometry (HRM) is typically performed for localizing the proximal border of the LES for placement of pH and pH-impedance catheters, which should be evaluated for the presence of major esophageal motor disorders, which can be associated with esophageal perceptible symptoms including heartburn and chest pain (Figure 1)³⁴. The prevalence of heartburn has been reported to be as high as 35% in achalasia^{35,36}; while this diagnosis can be suspected on upper endoscopy, diagnosis requires esophageal HRM. The presence of a minor motor disorder such as ineffective esophageal motility (IEM) does not preclude the diagnosis of functional heartburn, provided reflux disease has been excluded.

The most relevant and reliable parameter on ambulatory reflux monitoring is the percent time pH is less than 4 in the distal esophagus, termed the acid exposure time (AET). AET is considered to be reliably normal below 4% and abnormal above 6%³³. Abnormal AET has been reported in 26.3 to 72% of patients in refractory heartburn^{25,28,37-39}. Extending recording time to 48 or 96 hours with the wireless pH monitoring system increases the likelihood of detecting reflux disease : several studies have shown a highest diagnostic yield when the worst day is considered for the diagnosis of GERD, thus reducing the proportion of patients with functional heartburn³⁹⁻⁴¹.

Adding impedance to pH monitoring is helpful for the characterization of reflux episodes, as it allows detection of weakly acidic reflux episodes, thereby increasing the likelihood of a temporal correlation between symptoms and reflux episodes.⁴² Overall, studies performed with 24-hour pH-impedance monitoring report that between 21 to 40% of patients with refractory reflux symptoms have functional heartburn^{25, 28, 38, 43}. However, in patients studied “off” therapy, the added value of pH-impedance compared to pH alone monitoring is relatively limited^{43, 44}.

Both pH alone and pH-impedance monitoring provide analysis of the temporal relationship between reflux events and symptoms. In patients with normal AET, symptom index (SI) and symptom association probability (SAP) are used to distinguish between functional heartburn and reflux hypersensitivity. These indices reflect the occurrence of symptoms (i.e. activation of the event marker by the patient) and reflux events during the same 2-min time window. SI is a simple parameter which determines the proportion of symptoms that are reflux related (positive if > 50%). SAP uses a statistical formula, the Fisher exact test, which determines the probability that the observed temporal relationship between symptoms and reflux has not occurred by chance (positive if $\geq 95\%$). The two indices are complementary, but neither SI nor SAP are 100% reliable, and their relevance has been challenged by some authors, depending on frequency of symptoms and reflux occurrence⁴⁵. Functional heartburn can be reliably diagnosed in a patient with refractory heartburn, normal endoscopy and AET, and negative SI and SAP. Reflux hypersensitivity can be diagnosed if both SI and SAP are positive, but there is currently no consensus as to which should be taken into account if discrepancy exists between SI and SAP³³. The reflux-symptom association analysis is closely related to a proper performance of the reflux monitoring procedure and meticulous analysis protocols including careful selection of symptoms of interest. Patients must be instructed on how to use the event

marker and accurately fill in the symptom diary. A modification of the reflux-symptom association involves administration of acidic juice of known pH during pH monitoring to determine if symptoms can be elicited, and to evaluate pH recovery patterns which can distinguish between NERD and functional esophageal syndromes including functional heartburn⁴⁶.

Patients with proven GERD (evidenced by previous reflux esophagitis, Barrett's esophagus or abnormal pH monitoring) and persistent symptoms should be investigated on double dose PPI therapy with pH-impedance monitoring which allows the detection of weakly acidic reflux events. Overall, pH-impedance monitoring on therapy can establish a relationship between symptoms and acid reflux or weakly acidic reflux in 10% and 30 to 40% of patients, respectively^{38, 44, 47}, while negative studies are found in 50 to 60% of patients. Of note, some patients may have an overlap between GERD and functional heartburn. In these patients with an abnormal baseline AET, reflux monitoring should be performed on PPI therapy with pH-impedance monitoring. Diagnosis of functional heartburn overlapping with GERD is established if AET is normal and both SI and SAP are negative for both acid and weakly acidic reflux events, according to criteria introduced for the first time in ROME IV¹. Since this concept of overlapping GERD and functional disorders has been recently introduced^{1 11}, little is known about the clinical and psychological characteristics of these patients.

Additional metrics may be useful when the results of ambulatory reflux monitoring is borderline or inconclusive, e.g. if AET is between 4 and 6% or if discrepancies exist between SI and SAP. Mean nocturnal baseline impedance (MNBI) measured by pH-impedance tracings has been linked to mucosal damage⁴⁸. Some studies suggest that low MNBI (<2292 ohms), which functions as a surrogate marker of reflux-induced altered mucosal integrity, may help to

differentiate patients with reflux-related symptoms from patients with functional heartburn⁴⁹⁻⁵².

The post-reflux swallow-induced peristaltic wave (PSPW) index, i.e. the proportion of reflux episodes on pH-impedance monitoring followed by a swallow, reflects the integrity of primary peristalsis stimulated by reflux episodes⁵⁰. A normal PSPW index (>0.61) may help to distinguish patients with functional heartburn from those with GERD¹⁰. Considering the day-to-day variability and the lack of sensitivity of pH/pH-impedance studies, both MNBI and PSPW index may prove to be helpful for the management of patients with refractory heartburn but more data are needed to recommend the use of these metrics, including interobserver reproducibility, normal values and relevant cut-off values in clinical practice.

TREATMENT

While functional heartburn does not have long-term pathological consequences, the impact on patient quality of life can be substantial and very limiting. The treatment goals of functional heartburn are three-fold: 1) symptom improvement and, ideally, symptom resolution; 2) prevention of symptom recurrence; and 3) improvement of health-related quality of life. The main therapeutic modalities include lifestyle modifications, pharmacotherapy with neuromodulators, alternative and complementary medicine and psychological intervention (Table 1). A subset of patients may require more than one therapeutic modality for acceptable symptom control.

Lifestyle Modifications

There is limited evidence that improvement in quality of night time sleep can positively impact functional heartburn⁵, as increase in stressful activities including loud noise and sleep

deprivation can increase perception of esophageal symptoms^{53, 54}. Sleep disturbances have been identified as particularly common as heartburn and regurgitation symptoms increase in severity and frequency⁵⁵. Additionally, patients who report predictable and repetitive triggering of heartburn symptoms with certain food items or physical activities may benefit from avoiding these⁵⁶. However, there is no conclusive evidence that further lifestyle modifications have a role in functional heartburn in contrast to GERD.

Pharmacotherapy

Anti-reflux medications, specifically proton pump inhibitors have no therapeutic role in functional heartburn, unless there is an overlap between GERD and functional heartburn^{11, 57}. If such overlap is demonstrated on upper endoscopy and/or ambulatory reflux monitoring, PPI therapy can be maintained while targeted therapy for functional heartburn is initiated⁵⁸. If work-up demonstrates no conclusive evidence of GERD², an attempt to discontinue PPI therapy is warranted. An exception to this rule is H₂RAs, which may have an independent benefit in functional heartburn from an esophageal pain modulatory effect⁵⁹.

Neuromodulators have established value in the treatment of functional esophageal disorders, based on experience with noncardiac chest pain. Commonly used neuromodulators fall into the following categories: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin modulators (agonists and antagonists) and serotonin-norepinephrine reuptake inhibitors (SNRIs)^{58, 60}. Neuromodulators alter neuronal function without acting as neurotransmitters, with a primary central action and a minor secondary peripheral action on esophageal pain⁵⁸.

Several neuromodulators have been studied in functional heartburn (Table 2). In a double blind, placebo-controlled trial, 83 functional heartburn and reflux hypersensitivity patients were randomized to either placebo or imipramine 25 mg daily for a period of 8 weeks⁶¹. While there was no difference in improvement of heartburn between imipramine and placebo, there was significant improvement in quality of life with imipramine using per protocol analysis ($p=0.045$). Fluoxetine is the only SSRI studied in functional heartburn, where patients with persisting heartburn and negative endoscopy who failed standard dose once daily omeprazole were randomized to double dose omeprazole, add on fluoxetine 20 mg daily or add on placebo⁶². Those receiving fluoxetine demonstrated a significantly greater improvement in proportion of heartburn free days (median 35.7 days), as compared to those receiving double dose PPI (median 7.14 days, $p<0.001$) and placebo (median 7.14 days, $p<0.001$). This superior therapeutic effect of fluoxetine was seen only in the subset of patients with normal pH test.

In a double-blind, placebo-controlled trial, functional heartburn patients were randomized to tegaserod (a 5-HT₄ receptor partial agonist) at a 6 mg twice daily dose versus placebo for 14 days⁶³. Those receiving tegaserod tolerated higher balloon pressures ($p=0.04$) and maximum wall tension ($p=0.0004$) compared with placebo during balloon distension studies. Further, tegaserod significantly decreased the frequency of heartburn ($p=0.004$), regurgitation ($p=0.048$) and distress from regurgitation ($p=0.039$) compared to placebo, and with a higher global preference for tegaserod over placebo among the patients in the study.

The H₂RA ranitidine has been shown to have a pain modulatory effect by decreasing chemo-receptor sensitivity to esophageal acid perfusion at a dose of 150 mg daily in functional heartburn⁵⁹. However, certain brands of this medication is now subject to an FDA recall due to contamination with agents that may have a carcinogenic effect. Melatonin, which also has a pain

modulatory effect in the gastrointestinal tract, has demonstrated efficacy in various functional pain syndromes. In one study, functional heartburn patients randomized to receive melatonin 6 mg demonstrated a significant improvement in GERD health related quality of life, compared to nortriptyline 25 mg ($p=0.0015$) and placebo ($p<0.0001$) taken at bedtime for a period of 3 months⁶⁴.

Despite the limited numbers of trials assessing the value of neuromodulators in functional heartburn, these medications appear to have a therapeutic role, especially as first line therapy⁶⁵. Treatment with TCAs should follow the “low and slow” approach, where the lowest dose of TCA is initially used and increased by weekly increments of the same dose to a goal of 50-75 mg daily⁶⁰. These medications are commonly administered at bedtime because of somnolence, which in turn can improve patients sleep experience and augment their analgesic effect⁵⁴.

Alternative and Complementary Medicine

There are currently no studies that evaluated the primary role of various alternative and complementary medicine techniques in functional heartburn. However, in one small sample study of 30 heartburn patients who failed standard dose PPI and were randomized to add on acupuncture or double dose PPI, 10 acupuncture sessions over 4 weeks provided a significant decrease in the mean daytime heartburn, nighttime heartburn and acid regurgitation scores compared with those receiving double dose PPI⁶⁶. Mean general health score was significantly improved only in those receiving acupuncture. However, it is unclear what proportion of the study participants had functional heartburn, either solely or overlapping with GERD.

Psychological Intervention

Only hypnotherapy has been evaluated in patients with functional heartburn. In a very small study that included 9 functional heartburn patients, 7 weekly sessions of esophageal directed hypnotherapy were tolerated very well, with significant improvement in heartburn symptoms, visceral anxiety, quality of life and a trend toward improvement in catastrophizing⁶⁷.

Anti-reflux Surgery or Endoscopic Treatment

Both anti-reflux surgery and endoscopic treatment for GERD should be avoided in patients with functional heartburn. Normal pre-operative esophageal acid exposure has been shown to be a risk factor for poor outcome after surgical fundoplication^{68, 69}.

PROGNOSIS

Similar to other functional disorders, functional heartburn does not carry potential long-term complications, but is associated with reduced quality of life²². Since there can be overlap between true GERD and functional heartburn, and since a 24 hour ambulatory reflux monitoring study can miss abnormal esophageal acid exposure because of day to day variation⁷⁰, long term complications of GERD (Barrett's esophagus, peptic stricture) can potentially be identified in patients thought to have functional heartburn. However, this is anticipated to be rare, and the vast majority of patients with functional heartburn will have compromised quality of life rather than organic complications over time.

TABLE 1: THERAPEUTIC OPTIONS FOR FUNCTIONAL HEARTBURN

1. Lifestyle modifications
 - a. Improved sleep experience

2. Pharmacotherapy
 - a. Tricyclic antidepressants (TCAs)
 - b. Selective serotonin reuptake inhibitors (SSRIs)
 - c. Tegaserod
 - d. Histamine 2 Receptor antagonists (H₂RAs)
 - e. Melatonin

3. Alternative/complimentary Medicine
 - a. Acupuncture

4. Psychological intervention
 - a. Hypnotherapy

TABLE 2: NEUROMODULATOR TRIALS IN FUNCTIONAL HEARTBURN

Class	Drug	Dose	Number of Subjects	Outcome	Study Type
TCA	Imipramine	25 mg/d	83	<ul style="list-style-type: none"> No difference than placebo in symptom relief improved QOL 	RCT
SSRI	Fluoxetine	20 mg/d	144	<ul style="list-style-type: none"> Improvement in percentage of heartburn free days 	RCT
Serotonin Agonist (5-HT4)	Tegaserod	6 mg bid	42	<ul style="list-style-type: none"> Decreased frequency of heartburn, regurgitation and distress 	RCT
H ₂ RA	Ranitidine	150 mg	18	<ul style="list-style-type: none"> Decrease in esophageal sensitivity 	RCT
Miscellaneous anxiolytics, sedatives and hypnotics	Melatonin	6 mg bid	60	<ul style="list-style-type: none"> Improved GERD- HRQOL 	RCT

TCA – Tricyclics anti-depressant, SSRI- selective serotonin reuptake inhibitor, H₂RA – Histamine 2 receptor antagonist, HRQOL – Health related quality of life, RCT – randomized controlled trial.

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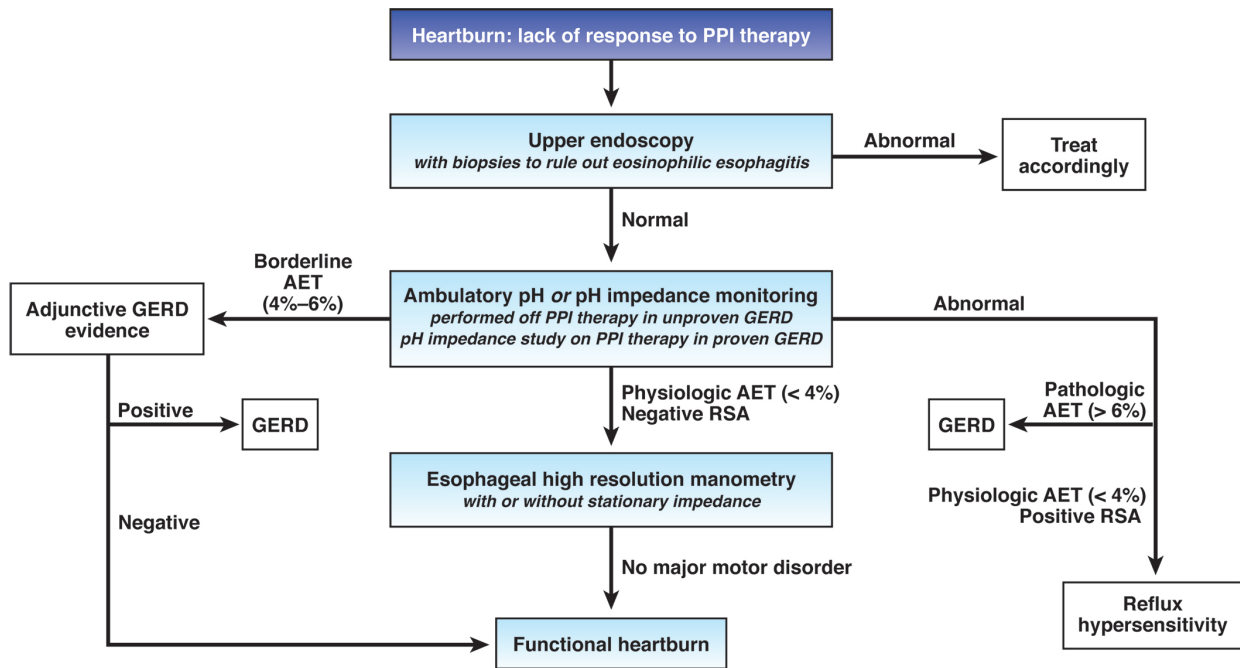
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FIGURE LEGEND

Figure 1. Flow diagram demonstrating evaluation of persisting heartburn symptoms despite maximal acid suppression. Endoscopy with biopsies to rule out eosinophilic esophagitis is the first step¹. Ambulatory reflux monitoring (either pH alone or pH-impedance monitoring) is performed off acid suppression in unproven GERD² (no prior esophagitis, Barrett's esophagus or peptic stricture, and no prior positive pH study), and on therapy in proven GERD. Functional heartburn is diagnosed when esophageal acid burden is physiologic (acid exposure time <4%), in the absence of esophageal mucosal disorders on endoscopy and major motor disorders on esophageal high resolution manometry¹. When acid exposure time is borderline (4-6%), absence of adjunctive reflux evidence (normal esophageal biopsies, normal baseline impedance >2292 ohms, normal PSPW index >0.61, negative reflux-symptom association, <40 reflux episodes, normal esophagogastric junction and esophageal body motor profile on high resolution manometry)² indicates the possibility of functional heartburn. Functional heartburn coexists with GERD in patients with proven GERD otherwise fulfilling criteria for functional heartburn.



AET, acid exposure time; RSA, reflux-symptom association; GERD, gastroesophageal reflux disease