

## Functional Esophageal Disorders

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Functional esophageal disorders represent processes accompanied by typical esophageal symptoms (heartburn, chest pain, dysphagia, globus) that are not explained by structural disorders, histopathology-based motor disturbances, or gastroesophageal reflux disease. Gastroesophageal reflux disease is the preferred diagnosis when reflux esophagitis or excessive esophageal acid exposure is present or when symptoms are closely related to acid reflux events or respond to antireflux therapy. A singular, well-defined pathogenetic mechanism is unavailable for any of these disorders; combinations of sensory and motor abnormalities involving both central and peripheral neural dysfunction have been invoked for some. Treatments remain empirical, although the efficacy of several interventions has been established in the case of functional chest pain. Management approaches that modulate central symptom perception or amplification often are required once local provoking factors (eg, noxious esophageal stimuli) have been eliminated. Future research directions include further determination of fundamental mechanisms responsible for symptoms, development of novel management strategies, and definition of the most cost-effective diagnostic and treatment approaches.

Functional esophageal disorders represent chronic symptoms typifying esophageal disease that have no readily identified structural or metabolic basis (Table 1). Although mechanisms responsible for the disorders remain poorly understood, a combination of physiologic and psychosocial factors likely contributes toward provoking and escalating symptoms to a clinically significant level. Several diagnostic requirements are uniform across the disorders: (1) exclusion of structural or metabolic disorders potentially responsible for symptoms is essential; (2) an arbitrary requirement of at least 3 months of symptoms with onset at least 6 months before diagnosis is applied to each diagnosis to establish some degree of chronicity; (3) gastroesophageal reflux disease (GERD) must be excluded as an explanation for symptoms; and (4) a motor disorder of the types with known

histopathologic bases (eg, achalasia, scleroderma esophagus) must not be the primary symptom source.

An important modification in threshold for the third uniform criterion has occurred in this reevaluation of the functional esophageal disorders.<sup>1</sup> Satisfactory evidence of a symptom relationship with acid reflux events, either by analytical determination from an ambulatory pH study or through subjective outcome from therapeutic antireflux trials, even in the absence of objective GERD evidence, now is sufficient to incriminate GERD (Figure 1). The purpose of this modification is to preferentially diagnose GERD over a functional disorder in the initial evaluation so that effective GERD treatments are not overlooked in management. Consequently, the acid-sensitive esophagus is now excluded from the group of functional esophageal disorders and considered within the realm of GERD, even if physiologic data indicate that hypersensitivity of the esophagus in this setting can encompass stimuli other than acid. Presumably symptoms that persist despite GERD interventions or that are out of proportion to the GERD findings ultimately would be reconsidered toward a functional diagnosis. The role of weakly acidic reflux events (reflux events with pH values between 4 and 7) remains unclear, and technological advances (eg, applications of multichannel intraluminal impedance monitoring) are expected to further define the small proportion with functional heartburn truly meeting all stated criteria.<sup>2</sup>

**Table 1.** Functional Gastrointestinal Disorders

A. Functional esophageal disorders
A1. Functional heartburn
A2. Functional chest pain of presumed esophageal origin
A3. Functional dysphagia
A4. Globus

*Abbreviations used in this paper:* GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

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## A1. Functional Heartburn

### Definition

Retrosternal burning in the absence of GERD that meets other essential criteria for the functional esophageal disorders typifies this diagnosis. Constraints in the ability to fully recognize the presence or importance of GERD in individual subjects likely result in a heterogeneous subject group.<sup>1</sup>

### Epidemiology

Heartburn is reported by 20%–40% of subjects in Western populations, depending on thresholds for a positive response. Studies using both endoscopy and ambulatory pH monitoring to objectively establish evidence of GERD indicate that functional heartburn represents <10% of patients with heartburn presenting to gastroenterologists.<sup>3</sup> The proportion may be higher in primary care settings.

### A1. Diagnostic Criteria\* for Functional Heartburn

Must include *all* of the following:

1. Burning retrosternal discomfort or pain
2. Absence of evidence that gastroesophageal acid reflux is the cause of the symptom
3. Absence of histopathology-based esophageal motility disorders

*\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.*

### Justification for Change in Diagnostic Criteria

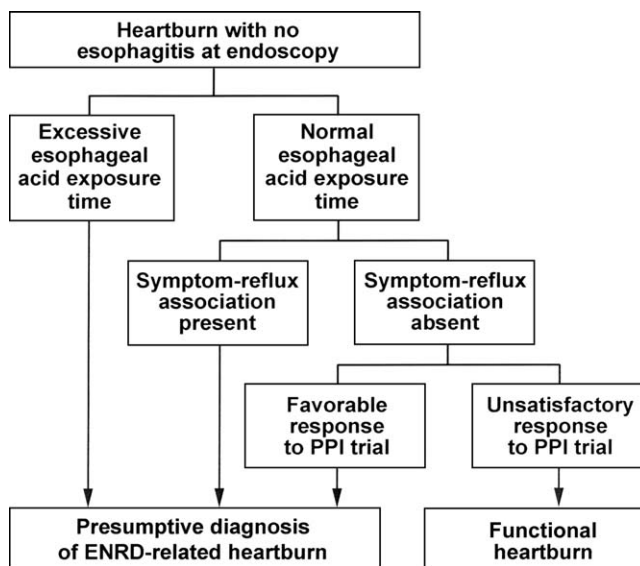
The threshold for the second criterion has been revised to exclude patients with normal esophageal acid exposure yet acid-related symptom events on ambulatory pH monitoring or symptomatic response to antireflux therapy. This group resembles other patients with GERD in terms of presentation, manometric findings, impact on quality of life, and natural history. Outcome is less satisfactory with antireflux therapy, however, and some subjects within this group will be shown to have functional symptoms that persist once their relationship to reflux events is eliminated with therapy.<sup>4</sup> Two or more days weekly of mild heartburn is sufficient in GERD to influence quality of life, but thresholds for symptom frequency or severity have not been determined for functional heartburn.<sup>5</sup>

### Clinical Evaluation

Clarification of the nature of the symptom is an essential first step to avoid overlooking extraesophageal symptom sources. Additional evaluation primarily is oriented toward establishing or excluding the presence of GERD.<sup>6,7</sup> Endoscopy that reveals no evidence of esophagitis is insufficient in this regard, especially in those subjects who are evaluated while remaining on or shortly after discontinuing antireflux therapy. Ambulatory pH monitoring can better classify patients who have normal findings on endoscopic evaluation, including those whose symptoms persist despite therapy. A favorable response to a brief therapeutic trial using high dosages of a proton pump inhibitor (PPI) is not specific,<sup>8</sup> but lack of response probably has a high negative predictive value for GERD.

### Physiologic Features

Much of the available literature is clouded by inclusion of subjects with undetected GERD in patient groups with presumed functional heartburn. The prevailing view is to consider disturbed visceral perception as a major factor involved in pathogenesis.<sup>9</sup> Enhanced sensitivity to refluxate having slight pH alterations from normal may be responsible in some instances. The focus has remained on intraluminal noxious stimulation; little direct evidence for alteration in central signal processing is available in these subjects with heartburn, although it is suspected.



**Figure 1.** Further classification of patients with heartburn and no evidence of esophagitis at endoscopy using ambulatory pH monitoring and response to a therapeutic trial of PPIs. The subset with functional heartburn has no findings that would support a presumptive diagnosis of endoscopy-negative reflux disease (ENRD). The precise thresholds for separation of subjects at each step remain uncertain. This figure shows classification categories by findings and is not meant to suggest a diagnostic management algorithm for use in clinical practice.

## Psychological Features

Acute experimental stress enhances perception of esophageal acid in patients with GERD without promoting reflux events.<sup>10</sup> Enhanced perception is influenced by the psychological status of the patient. Thus, psychological factors may participate in heartburn reporting when evidence of a noxious esophageal stimulus is limited. Psychological profiles do not differentiate subjects with normal esophageal acid exposure and no esophagitis from those with elevated acid exposure times, but patients whose heartburn does not correlate well with acid reflux events on an ambulatory pH study do demonstrate greater anxiety and somatization scores as well as poor social support than those with reflux-provoked symptoms.<sup>11</sup>

## Treatment

Persisting symptoms unrelated to GERD may respond to low-dose tricyclic antidepressants, other antidepressants, or psychological therapies used in many functional syndromes, although controlled trials demonstrating efficacy are unavailable. Reduction in transient lower esophageal sphincter relaxations with agents such as baclofen is being investigated.<sup>12</sup> Anti-reflux surgery in patients with functional heartburn and non-acid reflux events has not been fully evaluated, but surgical management would not be expected to be as beneficial as in GERD considering known outcome predictors for these operations.

## A2. Functional Chest Pain of Presumed Esophageal Origin

### Definition

This disorder is characterized by episodes of unexplained chest pain that usually are midline in location and of visceral quality and therefore potentially of esophageal origin. The pain easily is confused with cardiac angina and pain from other esophageal disorders, including achalasia and GERD.

### Epidemiology

Inferential data extracted from cardiac evaluations for chest pain indicate that this is a common disorder. Findings on 15%–30% of coronary angiograms performed in patients with chest pain are normal.<sup>13</sup> Although once considered a diagnosis of elderly women, chest pain without specific explanation was reported twice as commonly by subjects 15–34 years of age than by subjects older than 45 years of age in a

householders survey, and the sexes were equally represented.<sup>14</sup>

## A2. Diagnostic Criteria\* for Functional Chest Pain of Presumed Esophageal Origin

Must include *all* of the following:

1. Midline chest pain or discomfort that is not of burning quality
2. Absence of evidence that gastroesophageal reflux is the cause of the symptom
3. Absence of histopathology-based esophageal motility disorders

*\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

### Justification for Change in Diagnostic Criteria

As for other functional esophageal disorders, pain episodes linked to reflux events are now considered to fall within the spectrum of symptomatic GERD.

### Clinical Evaluation

Exclusion of cardiac disease is of pivotal importance. Likewise, identification of GERD as the cause of the symptom is essential for diagnostic categorization and management. Exclusion of GERD cannot rely on endoscopy alone, because esophagitis is found in <20% of patients with unexplained chest pain.<sup>15</sup> Ambulatory pH monitoring plays a useful role, and determining the statistical relationship between symptoms and reflux events is the most sensitive approach.<sup>16,17</sup> When combining subjects with and without abnormal acid exposure, 40% of patients with normal findings on coronary angiograms may have acid-related pain.<sup>1</sup> A brief therapeutic trial with a high-dose PPI regimen is a rapid way of determining clinically relevant reflux-symptom associations and is recommended for its simplicity and cost-effectiveness.<sup>18</sup> The diagnostic accuracy remains uncertain. Other diagnostic studies, including esophageal manometry, have a limited yield when chest pain is the sole symptom.

### Physiologic Features

Abnormalities have been detected in 3 categories: sensory abnormalities, distorted central signal processing, and abnormal esophageal motility. Motility abnormalities, particularly spastic motor disorders, are conspicuous, but their primary role in production of chest

pain is not well established. The relationship of recently observed sustained contraction of longitudinal muscle to pain is being studied. Enhanced sensitivity to intraluminal stimuli, including acid and esophageal distention, may be a primary abnormality. Patients with chest pain can be completely segregated from control subjects by pressure thresholds using impedance planimetry.<sup>19</sup> How subjects with functional chest pain reach the hypersensitivity state is not clear. Intermittent stimulation by physiologic acid reflux or spontaneous distention events with swallowing or belching may be relevant. Recent studies also verify alterations in central nervous system processing of afferent signals. A variety of investigational paradigms involving sensory decision theory, electrical stimulation and cortical evoked potentials, and heart rate variability indicate that chest pain reproduced by local esophageal stimulation is accompanied by errors in central signal processing and an autonomic response.<sup>20–22</sup> In acid-sensitive subjects, the findings are further provoked by acid instillation.

### Psychological Features

Psychological factors appear relevant in functional chest pain, with their role potentially being complex. Psychiatric diagnoses, particularly anxiety disorders, depression, and somatization disorder, are overrepresented in patients with chronic chest pain.<sup>23</sup> These disorders have not segregated well with specific physiologic findings, suggesting that they may interact toward producing the symptomatic state, possibly by mediating symptom severity and health care utilization.<sup>24</sup> Psychological factors also influence well-being, functioning, and quality of life, which are important outcomes in an otherwise nonmorbid disease.

### Treatment

Systematic management is recommended, because continued pain is associated with impaired functional status and increased health care utilization and spontaneous recovery is rare. Exclusionary evaluation including a therapeutic trial for GERD is indicated. Once the exclusionary evaluation is completed, management options for functional chest pain become limited. Smooth muscle relaxants are ineffective in controlled trials. Injection of botulinum toxin into the lower esophageal sphincter and esophageal body has had anecdotal use.<sup>25,26</sup> The most encouraging outcomes come from antidepressant and psychological/behavioral interventions.<sup>27,28</sup> Efficacy is demonstrated in controlled trials for both tricyclic antidepressants and more contemporary agents (eg, selective serotonin reuptake inhibitors).<sup>29,30</sup> Benefits have not been dependent on the presence of any particular

physiologic or psychological characteristic. Interest in a psychological intervention is reported by the majority of patients who are asked, particularly when activity limitation and pain intensity or frequency are high.

## A3. Functional Dysphagia

### Definition

The disorder is characterized by a sensation of abnormal bolus transit through the esophageal body. Thorough exclusion of structural lesions, GERD, and histopathology-based esophageal motor disorders is required for establishing the diagnosis.

### Epidemiology

Little information is available regarding the prevalence of functional dysphagia, largely because of the degree of exclusionary evaluation required. Between 7% and 8% of respondents from a householders survey reported dysphagia that was unexplained by questionnaire-ascertained disorders.<sup>14</sup> Less than 1% report frequent dysphagia. Functional dysphagia is the least prevalent of these functional esophageal disorders.

### A3. Diagnostic Criteria\* for Functional Dysphagia

Must include *all* of the following:

1. Sense of solid and/or liquid foods sticking, lodging, or passing abnormally through the esophagus
2. Absence of evidence that gastroesophageal reflux is the cause of the symptom
3. Absence of histopathology-based esophageal motility disorders

*\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

### Justification for Change in Diagnostic Criteria

Dysphagia is not easily linked to reflux events. Nevertheless, the modification of the threshold used for the second criterion (see the introduction) would attribute the symptom to GERD rather than a functional diagnosis if the link were established, even in the absence of other objective GERD indicators.

### Clinical Evaluation

Fastidious exclusion of structural disorders is required initially.<sup>31</sup> Endoscopy and esophageal barium ra-

diography are necessary to exclude intrinsic and extrinsic lesions, with radiographic studies being augmented with radio-opaque bolus challenge during fluoroscopy if required.<sup>32</sup> Biopsies at the time of endoscopy are recommended for excluding eosinophilic esophagitis. Esophageal manometry, primarily for detection of achalasia, is recommended if endoscopy and barium radiography fail to provide a specific diagnosis. Ambulatory pH monitoring plays a small role but may be helpful in patients whose dysphagia is associated with heartburn or regurgitation, but a brief therapeutic trial with a high-dose PPI regimen usually is satisfactory for identifying patients with subtle GERD as a cause for dysphagia.<sup>33</sup>

### Physiologic Features

Mechanisms responsible for this disorder are poorly understood. Peristaltic dysfunction may be responsible in some subjects. Rapid propagation velocity is accompanied by poor barium clearance that may be perceived as dysphagia.<sup>34</sup> Likewise, failed or low-amplitude contraction sequences impair esophageal emptying and can result in dysphagia.<sup>35</sup> Dysphagia also can be induced by intraluminal acid and balloon distention, suggesting that abnormal esophageal sensory perception may be a factor in some subjects.<sup>36</sup>

### Psychological Features

Acute stress experiments suggest that central factors can precipitate motor abnormalities potentially responsible for dysphagia.<sup>1</sup> Barium transit is adversely altered in asymptomatic and symptomatic subjects during recollection of unpleasant topics or stressful, unpleasant interviews. Noxious auditory stimuli or difficult cognitive tasks alter manometric recordings by increasing contraction wave amplitude and occasionally inducing simultaneous contraction sequences. The relevance of these findings to functional dysphagia remains conjectural.

### Treatment

Management includes reassurance, avoidance of precipitating factors, careful mastication of food, and modification of any psychological abnormality that seems directly relevant to symptom production. Symptom modulation with antidepressants and psychological therapies can be attempted, considering their effects in other disorders. Empirical dilation may be indicated.<sup>32</sup> Smooth muscle relaxants, botulinum toxin injection, or even pneumatic dilation can be useful in some patients with spastic disorders, particularly if incomplete lower esophageal sphincter relaxation and delay of distal esophageal emptying on barium radiography are evident.

## A4. Globus

### Definition

Globus is defined as a sense of a lump, a retained food bolus, or tightness in the throat. The symptom is nonpainful, frequently improves with eating, commonly is episodic, and is unassociated with dysphagia or odynophagia. Globus is unexplained by structural lesions, GERD, or histopathology-based esophageal motility disorders.

### Epidemiology

Globus is a common symptom and is reported by up to 46% of apparently healthy individuals, with a peak incidence in middle age.<sup>14</sup> It is uncommon in subjects younger than 20 years of age. The symptom is equally prevalent in men and women among healthy individuals in the community, but women are more likely to seek health care for this symptom.<sup>37</sup>

### A4. Diagnostic Criteria\* for Globus

Must include *all* of the following:

1. Persistent or intermittent, nonpainful sensation of a lump or foreign body in the throat
2. Occurrence of the sensation between meals
3. Absence of dysphagia or odynophagia
4. Absence of evidence that gastroesophageal reflux is the cause of the symptom
5. Absence of histopathology-based esophageal motility disorders

*\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

### Justification for Change in Diagnostic Criteria

By factor analysis, globus is distinct from pain, and pain often is indicative of a local structural disorder.<sup>38</sup> As for other functional esophageal disorders, demonstration that the symptom is directly related to reflux events would indicate a diagnosis of GERD, even in the absence of other objective evidence of GERD.

### Clinical Evaluation

The diagnosis is made from a compatible clinical history, including clarification that dysphagia is absent. Physical examination of the neck followed by nasolaryngoscopic examination of the pharynx and larynx are advised, although routine use of nasolaryngoscopy in patients with typical symptoms remains debated. Fur-

ther investigation of the simple symptom is not well supported; dysphagia, odynophagia, pain, weight loss, hoarseness, or other alarm symptoms mandate more extensive evaluation. There are grounds for a therapeutic trial of a PPI when uninvestigated patients present with the symptom of globus, particularly when typical reflux symptoms coexist.

### Physiologic Features

Consistent evidence is lacking to attribute globus to any specific anatomic abnormality, including the cricopharyngeal bar. Upper esophageal sphincter mechanics do not seem relevant, and the pharyngeal swallow mechanism is normal. Urge to swallow and increased swallow frequency might contribute to the symptom by periodically causing air entrapment in the proximal esophagus. Esophageal balloon distention can reproduce globus sensation at low distending thresholds, suggesting some degree of esophageal hypersensitivity.<sup>39</sup> Likewise, globus is more common in conjunction with reflux symptoms, although a strong relationship between GERD and globus has not been established.<sup>40</sup> Additionally, the symptom does not respond well to antireflux therapy. Although gastroesophageal reflux and distal esophageal motility disorders can include globus in their presentations, these mechanisms are believed to play a minimal role in the pathophysiology of globus.

### Psychological Features

No specific psychological characteristic has been identified in subjects with globus. Psychiatric diagnoses are prevalent in subjects seeking health care, but an explanation distinct from ascertainment bias has not been established. Increased reporting of stressful life events preceding symptom onset has been observed in several studies, suggesting that life stress might be a cofactor in symptom genesis or exacerbation.<sup>41</sup> Up to 96% of subjects with globus report symptom exacerbation during periods of high emotional intensity.<sup>42</sup>

### Treatment

Given the benign nature of the condition, the likelihood of long-term symptom persistence, and the absence of highly effective pharmacotherapy, the mainstay of treatment rests with explanation and reassurance. Expectations for prompt symptom resolution are low, because symptoms persist in up to 75% of patients at 3 years.<sup>43</sup> Controlled trials of antidepressants for globus are unavailable, but there is some anecdotal evidence for their utility.<sup>44</sup>

## Recommendations for Future Research

Despite their high prevalence rates, functional esophageal disorders have not been well studied. In particular, highly effective management approaches have not been established. Several areas requiring additional research were identified.

1. Studies validating the diagnostic criteria are needed, and a method for improving the accuracy of symptom-based criteria while limiting exclusionary workup would be welcomed.
2. The fundamental mechanisms of symptom production remain poorly defined. Further application of new technologies for measuring reflux events, motor physiology, and esophageal sensation as well as central signal modulation is recommended (eg, multichannel intraluminal impedance monitoring, high-resolution manometry).
3. Well-structured, controlled treatment trials would be welcomed in any of these disorders, because management remains highly empirical.
4. Treatment trials should include measures of quality of life and functional outcome when determining both short-term and long-term effects. The impact of interventions on functional impairment and health care resource use, important indicators of morbidity from the functional esophageal disorders, should be a focus in measuring treatment success.

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