Diagnosis of Symptomatic Gastroesophageal Reflux Disease

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ABSTRACT

Gastroesophageal reflux disease (GERD) encompasses a heterogeneous group of patients with differences in sensitivity to esophageal acid exposure, perception of pain, and physiological tissue involvement. The most difficult patients to understand are those who have a great symptom burden but no endoscopic evidence of esophageal mucosal involvement. These patients with symptomatic GERD (also called nonerosive reflux disease and endoscopy-negative reflux disease) present a diagnostic challenge. Diagnostic tests, like ambulatory pH monitoring, the acid perfusion test, and intraesophageal balloon distension, have limited reliability in patients with this form of GERD whose symptoms may exhibit poor correlation with acid exposure or mechano-stimulation. The recent interest in a proton pump inhibitor therapeutic trial to identify the group of symptomatic GERD patients (having ruled out risk factors for more morbid conditions) who will respond to these agents has considerable appeal. It has been shown effective in about 75% of patients, and offers a simple approach to managing the difficult-to-diagnose patient even while further diagnostic procedures are carried out. (Am J Gastroenterol 2003;98 Suppl.:S15–S23. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Gastroesophageal reflux disease (GERD) encompasses a broad spectrum of disorders defined by either reflux-related symptoms or complications of gastroesophageal reflux. In attempting to develop an all-encompassing definition, the Genval Working Group arrived at the following: “... all individuals who are exposed to the risk of physical complications from gastro-esophageal reflux or who experience clinically significant impairment of health-related well-being (quality of life) due to reflux-related symptoms ...” (1). Because our current focus is on the diagnosis of symptomatic GERD, also known as endoscopy-negative reflux disease and nonerosive reflux disease, we can ignore the physical complications (e.g., erosive esophagitis, Barrett’s esophagus) and focus on the remainder. Consequently, we are faced with the task of identifying individuals with “impaired quality of life due to reflux-related symptoms.” Thus, from a diagnostic viewpoint, the symptoms must be reflux related and the symptom burden must be to a degree that impairs quality of life (QOL). Applying this definition in clinical practice, three broad patient subgroups emerge: 1) patients with a pathophysiology similar to esophagitis but whose disease is undetectable by endoscopy; 2) patients with a symptom-based definition of GERD in whom a reflux causality can be established; and 3) patients with symptoms potentially related to symptomatic GERD but in whom a reflux causality cannot be established (functional heartburn). Let us first focus on the symptom profile of symptomatic GERD and its effect on QOL.

GERD SYMPTOMS AND EFFECT ON QUALITY OF LIFE

The most characteristic GERD symptoms are heartburn and acid regurgitation; heartburn is the most frequently encountered symptom of esophageal origin. Furthermore, given the high background prevalence of GERD in the United States, there is a very high predictive value of GERD as the diagnosis when heartburn is the dominant or exclusive symptom (2). Other common esophageal symptoms encountered in the symptomatic GERD population are regurgitation and chest pain. Although dysphagia, water brash, odynophagia, globus sensation, laryngitis, and hiccups are also potential symptoms of symptomatic GERD, discussion of these would go beyond the scope of the current treatise. One diagnostic pitfall of note is that because patients often misuse the term “heartburn” and/or refer to the intended symptom with other terms such as “indigestion,” it is incumbent on the clinician to clarify the intended meaning. The salient characteristics of heartburn and the other key esophageal symptoms are as follows.

Heartburn

Heartburn (pyrosis) is characterized by discomfort or a burning sensation behind the sternum that arises from the epigastrium and may radiate toward the neck. Heartburn is an intermittent symptom most commonly experienced within 60 min of eating, during exercise, and while lying recumbent. The discomfort is relieved with water or antacids but can occur frequently and interfere with normal activities (2).
Regurgitation

Regurgitation is the effortless return of esophageal or gastric contents into the pharynx without nausea or retching (2). Regurgitation of esophageal contents is characteristic of achalasia, whereas that of gastric contents is consistent with GERD. GERD patients note the presence of a sour or burning fluid in the throat or mouth that may also contain small undigested food particles. Bending, belching, or maneuvers that increase intra-abdominal pressure can provoke regurgitation. From a diagnostic perspective, the clinician needs to discriminate among regurgitation, vomiting, and rumination. Vomiting is preceded by nausea and accompanied by retching. Rumination is an acquired behavior in which mouthfuls of recently swallowed food are regurgitated and then reswallowed. This may be repeated for as long as an hour (2).

Chest Pain

This is a surprisingly common esophageal symptom with characteristics strikingly similar to cardiac pain, making discrimination between the two difficult in some instances. Given the potential for morbidity and mortality associated with cardiac pain, it is always appropriate to carefully consider a coronary etiology before evaluating for an esophageal cause. Esophageal pain is usually experienced as a pressure-like sensation in the mid-chest, radiating to the mid-back, arms, or jaws. The precise etiology of esophageal chest pain is unknown, but it is clearly overly simplistic to view this as indicative of esophageal spasm or a manifestation of a contractile abnormality. Rarely do such individuals objectively exhibit spasm and no correlation has been established between minor aberrations of esophageal contractility and pain events (3). More likely, the similarities to cardiac pain stem from the two organs sharing a nerve plexus and the nerve endings in the esophageal wall having poor discriminative ability among stimuli. Esophageal distention or even chemostimulation (e.g., with acid) will often be perceived as chest pain.

Quality of Life

Essentially all analyses of the impact of symptomatic GERD on QOL have focused on the frequency and severity of heartburn. With some reservation, the Genval Working Group accepted that “health-related well being is impaired in proportion to the frequency of heartburn” (1). Thus, the definition of symptomatic GERD ultimately becomes a quantitative issue. In attempting to define the quantitative limits of that definition, the Genval Working Group also accepted that “reflux disease is likely present when heartburn occurs on two or more days a week on the basis of the negative impact of this symptom frequency on health-related well being (QOL).” However, whereas the evidence in support of this first statement was generally well accepted by the experts and included well-designed cohort or case-controlled studies (4–7), about one quarter of the experts at the Workshop considered the evidence presented in support of the second statement insufficient (1). The hesitancy in accepting such a rigid definition is understandable because an average is just that: an average. In some cases, individuals are greatly troubled by a lesser symptom burden, whereas others trivialize a far greater one. Certainly, a decrement in perceived QOL occurs with a substantial reflux burden. This was illustrated by Revicki et al. (8), who compared Medical Outcomes Study Short-Form 36 (SF-36) data from individuals with moderate-to-severe reflux symp-
toms for at least 4 of 7 days before taking the survey with that observed in the general population (Fig. 1).

SYMPTOMATIC GERD PATIENT SUBGROUPS

Patients With Similar Pathophysiology to Esophagitis but Negative Endoscopy

Symptoms and complications of GERD result from excessive reflux of gastric contents, including acid and pepsin (normal gastric secretions), into the esophagus (1). However, despite being symptomatic, only a minority of heartburn sufferers will have esophagitis that is visible on endoscopy (9). Histological esophagitis appears as a thickening of the epithelial basal cell layer and elongation of the papillae in the distal esophageal mucosa, changes induced by accelerated shedding of the surface epithelial cells (10). On a cellular level, esophagitis is the result of hydrogen ion diffusion into the mucosa, leading to cellular acidification and necrosis (11). These changes ensue when the epithelial exposure to gastric juice exceeds the tolerance of that epithelium to resist such exposure. Implicit in this model is that some degree of exposure is normal and well tolerated. Thus, GERD symptoms are the result of a quantitative rather than a qualitative abnormality. Furthermore, the intermittent nature of GERD symptoms and esophagitis in many individuals suggests that this is often a rather delicately balanced system subject to a multitude of influences.

Considering the above construct, it becomes understandable that the endoscopic assessment of esophagitis utilizing a typical classification scheme such as the Los Angeles (LA) system will be imperfect. Missed diagnoses can result from intermittent findings not present at the time of endoscopy, subtle histopathological changes that are not part of the grading scale, or a consequence of the patient having been partially treated for what was previously erosive esophagitis. In cases such as this, the disease state fluctuates and in all likelihood, endoscopy at another time would reveal esophagitis or an ulcer, respectively. However, it appears that the majority of GERD patients initially negative upon endoscopy do not progress to develop erosive esophagitis with time (12).

With respect to the sensitivity of endoscopy in the detection of esophagitis, first consider the most standardized endoscopic grading system for esophagitis, the LA classification. In this scheme, minimal change, constituting LA grade A esophagitis, is of one or more mucosal breaks no longer than 5 mm that do not extend between the tops of two adjacent mucosal folds (13). An endoscopic mucosal break is defined as “an area of slough or erythema with a discrete line of demarcation from the adjacent, more normal looking mucosa.” Thus, the classification scheme ignores lesser endoscopic findings such as friability, red streaks, etc. The implication is that these lesser findings do not constitute esophagitis. In fact, the rationale for excluding them was simply that, in the developmental work leading to the LA classification, these changes proved not to be reproducible findings among endoscopists (13). Quite possibly, that conclusion would change with improved endoscopic technique, such as magnification endoscopy.

Evidence for this speculation can be found both physiologically and histologically. In a recent analysis of the histomorphological correlates of red streaks in the esophagus in patients with reflux disease, Vieth et al. (14) found that biopsies from such areas exhibited the papillae lengthened and the basal layers thickened analogous to the classic histological description of esophagitis made by Ismail-Beigi et al. (10). From a physiological perspective, Carlsson et al. were able to demonstrate an impaired mucosal barrier in symptomatic GERD patients, similar to that seen in esophagitis, by measurement of epithelial potential difference; the abnormality was reversible by effective antisecretory therapy (15).

Patients With a Reflux-Causality Established, Symptom-Based Definition of GERD

This is a complex patient subgroup encompassing individuals with typical and atypical reflux symptoms. Implicit in the definition is that endoscopic evidence of esophagitis is absent. Thus, the diagnosis could be based on the physiological demonstration of symptomatic reflux as might be achieved by ambulatory pH monitoring. The use and limitations of this approach and that of other physiological tests will be discussed in ESOPHAGEAL pH AND REFLUX SYMPTOMS. Alternatively, the diagnosis could be based solely on a symptom assessment. However, as was alluded to in the introduction, the mere presence of esophageal symptoms consistent with GERD does not equate to a demonstration that those symptoms are GERD related (instances in which causality cannot be established have been labeled “functional heartburn”; see ESOPHAGEAL pH AND REFLUX SYMPTOMS). One strategy adopted to address this limitation is adding the requirement of a beneficial therapeutic response to reflux treatment, the “proton pump inhibitor (PPI) test.” The merits of this approach will also be discussed in ESOPHAGEAL pH AND REFLUX SYMPTOMS.

ESOPHAGEAL pH AND REFLUX SYMPTOMS. Other than acid exposure time, GERD patients could potentially differ from normal volunteers (and each other) with respect to esophageal mucosal acid sensitivity, mucosal resistance to injury, the extent of mucosal acidification, or in the constituents of their refluxate other than acid. Furthermore, there is no “gold standard” for the definition of GERD in the absence of esophagitis. Therein lies the difficulty. It is easiest to evaluate the accuracy of data on pH monitoring comparing normal volunteers to patients with esophagitis, but that is not the population in which the clinician generally requires diagnostic help. To be clinically useful, esophageal pH monitoring must distinguish normal volunteers from
symptomatic GERD patients, as it is these individuals who represent a diagnostic problem.

Several investigators have compared the esophageal acid exposure time of normal volunteers with that of patients with esophagitis (16–19). These studies generally show a clear distinction between acid exposure times in the two populations and suggest that the discriminant ability of pH monitoring increases with the severity of esophagitis (16–19). Data pertaining to ambulatory pH monitoring in patients with symptomatic GERD are more rare and more variable (16–18), some describing increasing acid exposure with increasing symptoms and others showing no correlation between symptom severity and pH score. Furthermore, as might be predicted, these studies have shown less reproducibility and considerable overlap between the two populations (some with no clear separation) (Table 1) (16–18). Recognizing this, and that reflux events may cause symptoms regardless of the total acid exposure time, several schemes have been developed to analyze pH data in terms of symptom–reflux correlation, with the timing of symptoms indicated by activation of an event marker on the recording device.

Correlating symptoms with reflux events is immediately complicated by the observation that a one-to-one correlation between reflux events and symptoms does not exist. An elegant attempt at trying to distinguish the attributes of symptomatic reflux events from asymptomatic ones used multisite intraesophageal pH recording (20). The key findings of the study were that symptomatic events tended to be associated both with longer periods of esophageal acidification and with reflux episodes that acidified greater lengths of the esophageal epithelium.

Nevertheless, some manipulation of pH data are required to quantify the reflux–symptom relationship. The first attempt at this was the symptom index (SI), defined as the number of reflux-related symptom episodes divided by the total number of symptom episodes, expressed as a percentage (21). Although logical, the SI fails to consider the total number of reflux episodes. For example, if a patient had only one episode of chest pain during a 24-h study but happened to coincide with an episode of reflux, the SI would be 100%, even though 100 other episodes of reflux during the recording period may have been symptom free. The symptom sensitivity index (SSI), defined as the percentage of symptom-associated reflux episodes, was an attempt to circumvent this limitation (22). However, with both the SI and the SSI, a “positive” score is arbitrarily (as opposed to statistically) defined. On the other hand, the most recently developed scoring system, the symptom-association probability, statistically compares esophageal pH data temporally related to symptoms with pH data recorded during symptom-free episodes (23). The statistical approach uses contingency table analysis and Fisher’s exact test to analyze the four potential associations of pain and reflux: 1) reflux and pain; 2) reflux and no pain; 3) pain and no reflux; and 4) no reflux and no pain. However, it is imperative to recognize that all of these schemes of symptom–reflux correlation were devised from retrospective analyses of pH data and that none has been prospectively validated against an independent parameter of diagnostic accuracy.

THE ACID-SENSITIVE ESOPHAGUS. It has become evident that a poor parallel exists between symptom severity and either esophagitis severity determined by endoscopy or quantified esophageal acid exposure determined by esophageal pH monitoring. This recognition has led to the concept of the “acid-sensitive esophagus.” Several reports have identified patients with normal esophageal acid exposure during 24-h pH monitoring who nevertheless exhibit a strong temporal correlation between symptoms and reflux episodes (24, 25). Furthermore, the duration and minimum pH of symptom-provoking reflux events were shorter and higher, respectively, when compared with reflux episodes perceived by GERD patients with excessive acid exposure—suggesting that a subset of patients is, indeed, hypersensitive to acid (24). The efficacy of acid suppression therapy in these patients also supports the concept that, although part of the GERD disease spectrum, the key abnormality in these patients is that they are hypersensitive to esophageal acid reflux (4). Ambulatory pH data suggest that this subset represents a substantial fraction of symptomatic GERD patients (9). This discrepancy emphasizes that reflux symptoms and esophagitis have at least some independent determinants. Experimental data supporting this notion are summarized in THE BERNSTEIN TEST. Although several approaches have been used to provoke symptoms suggestive of esophageal disorders, the acid perfusion test and intraesophageal balloon distension (IEBD) are the two that are used most commonly in both clinical and research settings and discussion will be limited to them.

<table>
<thead>
<tr>
<th>Normal Range (Reference)</th>
<th>Symptomatic GERD Patients (Mean)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–7.2 (16)</td>
<td>5.8</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td>0–5.0 (18)</td>
<td>Grade 0: 1.9</td>
<td>0</td>
<td>100</td>
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<tr>
<td></td>
<td>Grade 1: 13.6</td>
<td>71</td>
<td>100</td>
</tr>
<tr>
<td>0–4.0 (17)</td>
<td>6.4</td>
<td>61</td>
<td>85</td>
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THE BERNSTEIN TEST. The Bernstein or acid perfusion test was introduced in 1958 by Bernstein and Baker to differentiate angina pectoris from esophageal pain (26). In general, 0.1 N HCl is instilled at a rate of 4–8 mL/min through a nasogastric tube with ports 5–15 cm proximal to the lower esophageal sphincter. During a separate, blinded portion of the test, isotonic saline is alternately instilled at the same rate, as a control condition. It is preferable to alternately infuse acid and saline at least twice, providing several opportunities to trigger heartburn symptoms during HCl administration and also making the symptoms come and go. The test is considered positive if the patient spontaneously perceives pain or burning during the acid instillation. Symptom relief during isotonic saline instillation is sometimes used as an additional positive test criterion. Although the traditional Bernstein test has been widely used, some modifications have been proposed. Smith et al. described a test in which a series of solutions of varied pH are infused (27). They found both a negative correlation between the percentage of patients complaining of pain and the pH of the infusate with this modification, and a positive correlation between the time to pain onset and pH of the infusate.

During the acid perfusion test, patient response is measured by qualitative or semiquantitative symptom assessment. Recently, three parameters have been proposed to quantify patient response further: 1) lag time (the time interval between onset of infusion and initial symptom perception, in seconds); 2) sensory intensity (the intensity of symptom perception at the end of acid perfusion, ranging from 0 to 20); and 3) an acid perfusion sensory score (lag time × intensity/100) (28, 29). The clinical significance of these parameters has yet to be determined.

The positive test rate of the acid perfusion test is always higher in typical GERD patients compared with healthy controls (30), suggesting that chronic acid exposure in these patients increases esophageal sensitivity to acid. This concept is also supported by an observed reduction in acid sensitivity after prolonged acid suppression therapy in patients with GERD, both with (31) and without esophagitis (32). In addition, the sensitivity of the Bernstein test for identifying patients with GERD is highly variable, ranging 42–100% among studies (33), perhaps because of differences in methodology (including GERD definition), patient selection, and criteria for a positive test. Further complicating the issue, patients with complicated GERD demonstrate reduced esophageal acid sensitivity and are more likely to have either a negative acid perfusion test or a higher threshold before the onset of symptoms than those with uncomplicated GERD (34).

INTRAESOPHAGEAL BALLOON DISTENSION (IEBD). IEBD was introduced even earlier than the Bernstein test. In 1955, this method was used in two studies to distinguish esophageal from cardiac chest pain (35, 36). At that time, the test received little attention. In 1986, the method was resurrected as a nonpharmacologic provocative test for chest pain (37). Although details may differ, most laboratories use a polyvinyl or latex balloon 10–30 mm long and 25 mm in diameter with 10 mL of air distension attached to a standard manometric catheter (35). The catheter is positioned with the balloon located 10 cm above the lower esophageal sphincter, and the balloon is distended in a stepwise fashion, 1 mL at a time, with each step maintained for 10 s. To eliminate the effect of accommodation, the balloon is completely emptied for 5 s between each incremental volume increase. A positive response is recorded when the subject complains of chest pain. Subsequent analyses have shown that the distending diameter, rather than pressure, is the critical factor for stimulating pain, that the thresholds for sensation and pain are significantly lower with rapid distension, and that sustained distension increases the level of sensory awareness (38).

One criticism of the IEBD test is that it relies on the subject reporting pain while they are focusing on that sensation. As such, it is influenced by many factors, including subject cooperation, physiological and psychoaffective parameters (depression, anxiety, etc.), cultural values, and personal experience. As an alternative, the recording of cerebral evoked potentials in response to esophageal stimulation provides objective information on the sensation of esophageal pain and appears to be a useful tool to study the afferent pathways from the esophagus. Recently, several new techniques including magnetoencephalography, positron emission tomography, and functional magnetic resonance imaging (fMRI) have also been used to both localize and quantify the central nervous system response to different esophageal stimuli (39). With fMRI, the cortical response to distension has been shown to occur in the same regions as that for acid perfusion with a latency of only about 5 s compared with 5 min for acid perfusion (40).

Thresholds for sensation and pain during IEBD differ from one study to another (37, 39, 40). Various differences in subject groups (age, gender, and height), balloon properties (size, shape, and composition) and inflation technique (rapid versus slow) may account for some of these discrepancies. For example, younger subjects and women are more sensitive to mechanical stimulation of the esophagus (41). The location of the balloon is also important, as the proximal esophagus is more sensitive to IEBD than the distal esophagus (42, 43).

Minimal data exist regarding the sensitivity to IEBD in typical GERD patients. Clouse et al. analyzed a heterogeneous group of patients referred for esophageal motility testing and found that esophageal motor and sensory dysfunction were correlated, suggesting that both may contribute to symptomatology (41). Trimble et al. found an inverse correlation between the severity of esophagitis and esophageal sensitivity, such that symptomatic patients without excess reflux were the most sensitive and patients with Barrett’s esophagus were least sensitive (44). The IEBD sensitivity level of patients with excess reflux ranked in
between these two groups and was similar to that of healthy controls. Fass et al., on the other hand, found no significant correlation between esophagitis severity and the thresholds for pain or discomfort on IEBD (31).

Further exploring the concept of generalized hypersensitivity, Trimble et al. used IEBD to compare patients with hypersensitivity with healthy volunteers, typical GERD patients, and patients with Barrett’s esophagus and found that patients who were acid hypersensitive also had the highest sensitivity to mechanical stimulation (44). Consistent with this finding, acid-hypersensitive patients exhibited the greatest sensitivity to both acid perfusion and IEBD (45), whereas typical GERD patients had a higher sensitivity to acid but not to IEBD as compared with healthy controls (41, 45). These findings support the concept of “irritable esophagus” in the hypersensitive group of patients (46).

THE “PPI TEST.” Several recent, prospective, controlled trials have examined the utility of empirical treatment with PPIs in the diagnosis of GERD (47–49). These studies reported a sensitivity for the “PPI test” of 68%–80% for the diagnosis of GERD defined by either endoscopic erosive esophagitis or an abnormal pH monitoring test. One study reported the sensitivity and specificity of the “PPI test” to be comparable to pH testing (49). In interpreting these studies, it is important to note that the sensitivity of any PPI test is dependent upon how one defines a positive test and exactly what is achieved by a “positive test” in terms of patient management.

To put things in perspective, the fact that PPI therapy is effective does not diagnose GERD any more than a beneficial response to aspirin diagnoses arthritis. On the other hand, each treatment provides effective symptomatic therapy for a family of conditions and determining that they are efficacious may obviate the need for a more specific diagnosis. Clearly, a 2-wk trial of a PPI in patients with symptoms suggestive of GERD identifies a substantial proportion of patients responsive to the therapy but who would not otherwise be identified by any available diagnostic test. There is no doubt that establishing that therapeutic response is useful information in managing such patients but, in and of itself, it neither establishes their diagnosis, nor identifies their optimal therapy.

Given that the object of therapy is symptom relief, there is great appeal to the concept of a therapeutic trial. What better way of detecting individuals with symptoms who will respond to antisecretory therapy than to render that therapy and gauge the response? A PPI is an ideal agent to use in such a trial because of its proven efficacy in treating all acid-related disorders, including GERD. However, knowing that someone responds to a given PPI regimen does not equate to a diagnosis of GERD any more than their not responding to this regimen rules it out. In the case of the responder, the symptom–reflux association and/or endoscopic findings establish the diagnosis. If these are equivocal, we might just as well call the disease nonulcer dyspepsia. In the case of the nonresponder, it could be an instance in which this therapy is inadequate, or it could be that the presumptive diagnosis is incorrect. Treatment failures may occur with atypical symptoms of reflux, esophageal hypersensitivity, functional heartburn, or extraesophageal manifestations of the disease. Each of these scenarios represents a treatise in its own right but, clearly, the logical first step in management is to identify the large set of individuals who do respond to straightforward therapy.

Patients With Functional Heartburn
To quote from the Rome II definitions regarding functional GI disorders, “functional esophageal disorders represent chronic symptoms that typify esophageal disease yet have no identifiable structural or metabolic basis” (50). Functional heartburn is defined as “episodic burning in the absence of pathological reflux, pathology-based motility disorders, or structural explanations.” The term still can be applied to those patients whose symptoms are associated with acid reflux events during ambulatory pH monitoring, provided the duration of esophageal acid exposure is normal (50). Obviously, there is an inconsistency in these definitions, which more than likely reflects the difficulty of the task. For the purposes of the present discussion, we have already considered the hypersensitive population and will consider the remainder to constitute the functional heartburn group.

Once the symptomatic GERD patient groups with “undetected esophagitis” and visceral hyperalgesia are removed, we are left without a physiological explanation for symptoms. Meaningful data in this population of functional heartburn patients are essentially nonexistent. Given that, one cannot discount the role played by psychosocial factors. Early life experiences and influences may modify a patient’s perception and interpretation of esophageal symptoms. A higher frequency of physical and sexual abuse has been reported among patients with functional GI disorders in general (51). Patients with chest pain with a normal cardiac evaluation who are deemed to have a weak social support structure demonstrated poor correlation between symptom complaints and acid reflux events on ambulatory pH monitoring (52). Consistent with this, many patients report that heartburn symptoms are increased and/or more frequent during times of psychological and emotional stress. However, studies have demonstrated no significant quantitative difference in acid reflux in these patients during stressful events (51, 52). It has been proposed that these patients may have a psychological tendency to report more symptoms than the general population and that anxiety in these individuals may lead to cortical amplification of low-to-moderate intensity afferent signals from esophageal receptors (51). Finally, it is worth noting that various psychiatric disorders, such as depression, obsessive-compulsive behavior, somatization, and anxiety disorders, are more prevalent in these patients (53, 54).
As it is apparent that psychological factors play a role in esophageal chest pain, antidepressant medications have been used in the treatment of patients with esophageal hyperalgesia, including those who complain of chest pain (55). These agents have been found to reduce chest pain in symptomatic patients with esophageal contraction abnormalities (56). However, in other studies, this approach has yielded somewhat conflicting results. Imipramine was found to significantly raise the threshold for pain but not sensation to IEBD in normal males (57). In another study, amitriptyline had no effect on the perception of esophageal distension despite a significant effect on the perception of somatic electrical stimulation (58). It should be noted, however, that these results were obtained in healthy controls, and no data currently exist on the modification of esophageal sensitivity in disease states.

**CONCLUSION**

Symptomatic GERD may be defined by the absence of physical consequences of gastroesophageal reflux and the occurrence of reflux-related symptoms significant enough to impair the individual’s perceived QOL. Applying this definition in clinical practice, three broad patient subgroups emerge: 1) patients with a pathophysiology similar to esophagitis but whose disease is undetectable by endoscopy; 2) patients with a symptom-based definition of symptomatic GERD in whom reflux causality can be established; and 3) patients with symptoms potentially related to symptomatic GERD but in whom reflux causality can not be established (functional heartburn). Included in the second subgroup are patients with acid hypersensitivity and those with atypical manifestations of GERD. With respect to the third group, one can easily argue that these individuals do not have GERD at all, but rather have underlying psychosocial factors at the root of their symptomatology. However, they are typically grouped with the symptomatic GERD population because of the difficulty of distinguishing them from the second group.

Another way to categorize GERD patients is to look at acid and mechanosensitivity of the three populations (Fig. 2): patients with normal acid and mechanosensitivity, patients who are universally hypersensitive, and patients who are uniquely acid sensitive (45). From a clinical vantage point, we have excellent therapies only for chemosensitivity. Thus from a very pragmatic viewpoint, once it is ascertained that the patient does not have significant risk factors for more morbid conditions, there is great appeal in the use of a PPI therapeutic trial as an early intervention to identify the large fraction of symptomatic GERD patients who will experience a beneficial response from these agents. The relevance of identifying the specific pathophysiology responsible for symptomatic GERD in the remainder of patients, and indeed whether many of the remainder of patients should even be categorized as having symptomatic GERD, is debatable.

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Received Nov. 1, 2002; accepted Dec. 18, 2002.
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