The Effect of Auditory Stress on Perception of Intraesophageal Acid in Patients With Gastroesophageal Reflux Disease

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Background & Aims: **Most patients with gastroesophageal reflux disease (GERD) report that stress exacerbates their symptoms, yet mechanisms underlying this association remain unknown. We sought to determine the effect of an acute laboratory stressor on perceptual and emotional responses to intraesophageal acid perfusion in healthy controls and patients with GERD.** ***Methods:*** **Forty-six patients with heartburn and 10 healthy controls underwent upper endoscopy and, if negative, pH monitoring. Assessment of psychologic factors and health-related quality of life was done by a questionnaire. Perceptual and emotional responses to intraesophageal acid at baseline, during auditory stress, and during an auditory control condition were determined using a randomized crossover design. Plasma levels of norepinephrine, adrenocorticotropic hormone, and cortisol were assessed.** ***Results:*** **Twenty-nine subjects were identified as nonerosive reflux disease and 17 as erosive esophagitis. Quality of life, psychologic profile, and personality assessment variables were similar among the 2 patient groups and the controls. There was a significant reduction in mean lag time to initial symptom perception and an increase in mean intensity rating and mean acid perfusion sensitivity score in the 2 patient groups during the stress period, which was not seen during the control condition. Healthy controls demonstrated lack of a significant change in all parameters of stimulus response functions to acid, regardless of condition.** ***Conclusions:*** **Acute auditory stress can exacerbate heartburn symptoms in GERD patients by enhancing perceptual response to intraesophageal acid exposure. This greater perceptual response is associated with greater emotional responses to the stressor.**

Heartburn is the cardinal symptom of gastroesophageal reflux disease (GERD) that can result from either acute or chronic esophageal acid exposure. Based on animal models and human studies of afferent nerve sensitization, acute or chronic acid exposure can sensitize esophageal afferent pathways resulting in symptom generation in GERD. The peripheral sensitization can occur directly (by activation of acid sensing ion channels) or via esophagitis-associated inflammatory mediators.[1,2] The development of central (spinal) sensitization underlying the sensitizing effect of acute acid exposure has been demonstrated in healthy subjects.[3] The degree of central sensitization can be modulated by factors other than acid exposure. For example, preliminary results suggest that anxiety may play a modulatory effect on sensitization.[4]

GERD represents a spectrum of symptoms as well as spectrum of altered pain perception to acid. For example, patients with Barrett's esophagus, a complication of advanced, long-standing GERD, have demonstrated reduced chemoreceptor sensitivity to acid perfusion and mechanoreceptor sensitivity to balloon distention.[5–8] In contrast, many patients with functional heartburn, in whom esophageal inflammation or excess of esophageal acid exposure is not detectable, appear to have increased perceptual sensitivity to both acid infusion and balloon distention when compared with patients with documented increase in esophageal acid exposure.[5,9] The mechanism underlying altered pain perception in these GERD groups is incompletely understood but is likely to involve both peripheral and central modulatory factors.

Psychosocial factors, including stress, may play an important role in symptom generation in GERD. In a Gallup Poll, 64% of individuals with heartburn reported that stress increased their symptoms.[10] Despite these findings, very few studies have assessed the effect of stress on perception of visceral stimuli (referred from here on as "visceral sensitivity") and specifically on esophageal sensitivity. A substantial subset of patients with GERD demonstrates psychologic disturbances such as depression, anxiety, somatization,[11–13] which may interact with environmental stress to produce increased perceptions of reflux symptoms, even in the absence of concomitant

Abbreviations used in this paper: ACTH, adrenocorticotropic hormone; GERD, gastroesophageal reflux disease; HRQOL, health-related quality of life; EE, erosive esophagitis; NE, norepinephrine; NERD, nonerosive reflux disease.

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increase in esophageal acid exposure.[14,15] Major life stressors have been shown in a longitudinal study to predict symptom exacerbations in patients with heartburn.[16] Interventions aimed at reducing stress in patients with GERD (eg, hypnosis, progressive muscle relaxation technique) have been shown to result in subjective improvement in reflux symptom ratings and significant reduction in total esophageal acid exposure.[14] These findings support the emerging concept that, similar to its role in modulating symptom generation in functional gastrointestinal disorders, brain-gut interactions are important in symptom perception and physiologic responses in the esophagus of patients with GERD.[17–19]

In contrast to the large number of studies on stress modulation of gastrointestinal function, the effect of stress on esophageal symptoms, motility, and pain perception has rarely been studied.[20–23] Interpretation of earlier studies is limited by lack of direct evidence that acid exposure in stressed GERD patients is associated with higher perceptual responses to intraesophageal acid as compared with nonstressed GERD patients. Furthermore, data about the effect of stress on different GERD populations, such as nonerosive reflux disease (NERD) and erosive esophagitis (EE), are lacking. This is particularly important in the former group because NERD patients have altered pain perception to acid perfusion.[24] Thus, the aim of the current study was to determine the effect of an established acute psychologic stress condition on perceptual and emotional responses in healthy controls and patients with established GERD, subclassified as NERD and EE. Specifically, we wanted to test the following hypotheses: (1) Psychologic stress increases conscious perception of intraluminal acid stimuli; (2) this stress-induced pain facilitation may play a greater role in patients with NERD; and (3) stress-induced pain facilitation may be greatest in patients with increased level of anxiety.

Materials and Methods

Subjects

Forty-six consecutive patients with typical GERD symptoms (heartburn and acid regurgitation) at least twice a week were recruited into the study. Both patients with or without esophageal mucosal injury were included. Exclusion criteria included previous gastrointestinal surgery; active peptic ulcer disease; Barrett's esophagus; autonomic or peripheral neuropathy; myopathy; diabetes mellitus; irritable bowel syndrome; use of tricyclics, selective serotonin reuptake inhibitors, narcotics, or benzodiazepines; or any other disease or medication that may affect symptoms perception, lower esophageal sphincter basal pressure, or acid clearance time. In addition, 10 healthy, normal subjects were recruited for controls. None of the control subjects had any GERD symptoms, and none had ever used antireflux treatment. The Human Subject Committee of the University of Arizona approved this study.

Protocol

All subjects with heartburn who agreed to participate in the study signed informed consent. Patients with GERD underwent upper endoscopy, and those with documented mucosal inflammation were enrolled into the EE group. The remainder of patients with normal upper endoscopy underwent ambulatory 24-hour esophageal pH monitoring and was considered as having nonerosive reflux disease. Patients with normal endoscopy and esophageal acid exposure within normal range were excluded from the study. Demographics were obtained by personal interview. Symptoms frequency and severity were assessed by the GERD symptom questionnaire, health-related quality of life by the Short Form 36 (SF-36), personality inventory by the Minnesota Multiphasic and Personality Inventory (MMPI-2), and psychologic profile by the Symptom Checklist-90 Revised (SCL-90R). Subjects were then referred to the physiology laboratory for stress induction.

On day 1, subjects initially completed the stress symptom rating questionnaire (SSR), which assesses current mood. Plasma levels were obtained for adrenocorticotropic hormone (ACTH), cortisol, and norepinephrine (NE). Subsequently, a tube with a central lumen was placed in the midesophagus, and baseline acid perfusion test was performed. At the end of the acid perfusion, the SSR was repeated, and blood was again obtained for ACTH, cortisol, and NE levels. Subsequently, subjects underwent a washout period for 30 minutes. Subjects were then randomized to either stress induction or control period. Prior to randomization, the SSR was again repeated. After completion of either the stress induction or the control period, the SSR was again completed by the subjects, and blood was obtained for ACTH, cortisol, and NE levels. On day 2, the experiment was initiated at the same time as the first experiment to control for normal fluctuations in serum hormonal levels. Initially, subjects underwent the SSR questionnaire, followed by blood collection for ACTH, cortisol, and NE levels. A tube with a central lumen was then placed in the midesophagus. Per previous randomization, subjects were crossed over to the other arm. At the end of the experiment, the SSR was again completed by the subjects, and blood samples were collected for ACTH, cortisol, and NE levels. Perceptual stimulus ratings were obtained at the end of acid perfusion. Figure 1 summarizes the procedures for each experimental session.

Symptom Severity Assessment

All subjects enrolled in the study completed a validated GERD symptom questionnaire, which assesses the occurrence of heartburn, acid regurgitation, chest pain, dysphagia,[25] and the influence of GERD symptoms