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Response of the Upper Esophageal Sphincter to Esophageal Distension Is Affected by Posture, Velocity, Volume, and Composition of the Infusate

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BACKGROUND & AIMS: Studies of the pressure response of the upper esophageal sphincter (UES) to simulated or spontaneous gastroesophageal reflux have shown conflicting results. These discrepancies could result from uncontrolled influence of variables such as posture, volume, and velocity of distension. We characterized in humans the effects of these variables on UES pressure response to esophageal distension. **METHODS:** We studied 12 healthy volunteers (average, 27 ± 5 years old; 6 male) using concurrent esophageal infusion and high-resolution manometry to determine UES, lower esophageal sphincter, and intraesophageal pressure values. Reflux events were simulated by distal esophageal injections of room temperature air and water (5, 10, 20, and 50 mL) in individuals in 3 positions (upright, supine, and semisupine). Frequencies of various UES responses were compared using χ^2 analysis. Multinomial logistical regression analysis was used to identify factors that determine the UES response. **RESULTS:** UES contraction and relaxation were the overriding responses to esophageal water and air distension, respectively, in a volume-dependent fashion ($P < .001$). Water-induced UES contraction and air-induced UES relaxation were the predominant responses among individuals in supine and upright positions, respectively ($P < .001$). The prevalence of their respective predominant response significantly decreased in the opposite position. Proximal esophageal dp/dt significantly and independently differentiated the UES response to infusion with water or air. **CONCLUSIONS: The UES response to esophageal distension is affected by combined effects of posture (spatial orientation of the esophagus), physical properties, and volume of refluxate, as well as the magnitude and rate of increase in intraesophageal pressure. The UES response to esophageal distension can be predicted using a model that incorporates these factors.**

Keywords: Esophagus; Stomach; Airway; GERD.

Gas, liquid, and their mixture are the main components of gastroesophageal reflux (GER). The consequence of their entry into the pharynx in terms of airway safety and potential aspiration is quite different, especially during sleep. Over the past century, a number of reflexes emanating from the esophagus have been identified, such as secondary peristalsis,[1] upper esophageal sphincter (UES) contraction,[2] and closure of the vocal cords,[3] which in isolation or in combination through different mechanisms protect the airway against aspiration of gastric contents. The function of the human UES in response to esophageal distension either by a balloon or simulated GER using esophageal perfusion of air and liquid or spontaneous GER has been studied extensively for more than 50 years.[2–15] Although some of these studies reported a UES contraction response to esophageal distension with a balloon,[2,11,15] nonacid and acid liquid,[2,4,12,13] and esophageal common cavity,[6] these observations have been challenged by studies that either did not show a UES contraction response[7,14] or observed UES relaxation[5] during simulated or spontaneous esophageal acid exposure.

Center to the complexity of the UES response to reflux events is the variable physical properties of the refluxate and the influence of posture on its impact, which eludes quantification and qualification during studies of naturally occurring reflux episodes. Other factors such as technical difficulties in measuring UES pressure in some studies due to the axial movement of the sphincter, hydrostatic effects of perfused systems, and inherent differences in fidelity of recording technique may have contributed to the discrepancies observed among various studies. Some investigators have correlated the UES response to transient lower esophageal sphincter relaxation (TLESR) but have ignored the fundamental effect of change in intraesophageal pressure and its associated esophageal wall tension due to distension on UES pressure.[5] Others have used common cavity as a surrogate marker of GER without incorporating the effect of the physical properties of the reflux material, which have caused increased intraesophageal pressure.[6] These shortcomings have resulted in confusing and at times contradictory findings.

Abbreviations used in this paper: GER, gastroesophageal reflux; OR, odds ratio; TLESR, transient lower esophageal sphincter relaxation; UES, upper esophageal sphincter.

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A recent report investigating postprandial GER episodes during TLESR in humans showed that the physical properties of the refluxate and the posture of subjects correlated with the type of UES response.[16] The majority of GER episodes in the recumbent posture contained liquid only and were associated with UES contraction. In contrast, GER episodes in the upright posture mainly contained air component and were coupled with UES relaxation. Furthermore, it was proposed that the rate of esophageal pressure increase could have been the distinctive factor for the differing UES response to GER episodes.[16] However, volume and physical properties of the refluxate could not be controlled in this study, and therefore it was difficult to determine whether the subject's posture, the physical property of refluxate, or the magnitude and the rate of the increase in esophageal pressure were the determinants of the UES response.[16]

The present study aims to test the unifying hypothesis that UES pressure response to GER is multifactorial and is influenced by physical property and volume of the distending agent, spatial orientation of the esophagus, and the velocity and magnitude of its distension.

Subjects and Methods

Study Protocol

We enrolled 12 healthy young volunteers (27 ± 5 years, 6 female). The Institutional Review Board Committee of the Medical College of Wisconsin approved the study protocol, and each subject provided both verbal and written consent before enrollment in the study. They had no history of known gastrointestinal disorders and were not taking any medications that may have affected the gastrointestinal tract. Transnasal endoscopy was performed in all subjects before the study and showed no erosive esophagitis or other luminal abnormalities of the esophagus, gastroesophageal junction, and stomach.[17] Subjects were comfortably studied in a powered medical examination chair with stretched legs in upright, supine, and semisupine (45°) postures. Following 6 hours of fasting and topical lidocaine application, a solid-state high-resolution manometry catheter with 36 circumferential pressure sensors, spaced 1 cm apart (Sierra Scientific, Los Angeles, CA), was introduced transnasally in a fashion that at least 3 proximal sensors were located in the pharynx. Subsequently, a 3-mm OD injection tube was placed through the same nostril in a fashion that the injection port was located 5 cm above the upper border of the lower esophageal sphincter (LES). GER events were simulated by intraesophageal injection of room air and tap water (allowed to acclimate to room temperature for 30 minutes) uniformly by a single operator (A.B.) using a 60-mL syringe. Exact timing and type of the injection were documented by the second investigator (J.L.) using the event marker feature of the Manoscan system (Sierra Scientific, Los Angeles, CA). The rate of perfusion was evaluated in vitro by a series of trials recorded on a Narco Bio-Systems MMS 200 (Austin, TX) physiologic recorder showing a rate of 50 mL/s for air and 10 mL/s for water injections. We tested 3 trials of 5-, 10-, 20-, and 50-mL volumes of each substance in a random order, resulting in 72 events for analysis in each subject. Each perfusion was only performed when the UES, esophagus, and LES were at baseline for at least 3 tidal volume respiratory cycles and 20 seconds after a preceding peristaltic event. After each perfusion, manometry was carefully monitored for 20 seconds and then subjects were cued to swallow and clear esophageal contents. Esophageal clearance was confirmed by an effective peristaltic wave and return of intraesophageal pressure to baseline. All volunteers tolerated the procedure except for one who reported minor nausea during injection of 50 mL of liquid while in the supine position but was able to finish the protocol in another session.

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Pressure Data Analysis

All pressure measurements were recorded at a 35-Hz frequency and measured in reference to the atmospheric pressure (except LES, which was measured in reference to gastric pressure). UES and LES pressures were measured using the e-sleeve function of the Manoview software (Sierra Scientific). All UES, LES, and esophageal baseline pressures were measured as peaks and troughs over 3 tidal volume respiratory cycles at stable resting conditions when no pharyngeal, gastric, esophageal, UES, or LES events were present. Type, frequency, amplitude, onset, and duration of the UES response along with the LES and esophageal body response were recorded. All responses were determined in a 10-second window after the injection. Percent UES relaxation and percent UES contraction were calculated as a fraction of the maximum possible relaxation (baseline UES pressure – proximal esophageal pressure) and as a fraction of the maximum UES contraction pressure, respectively. UES relaxation was considered complete (100%) if an audible belch was documented or the nadir UES pressure equalized to the proximal esophageal pressure. Because of considerable variability of the resting UES pressure even at rest, we decided to set a conservative threshold (10 mm Hg) for determining the UES response.[5,16] UES response was categorized as an ordinal variable: contraction (UES pressure exceeded the peak baseline pressure by more than 10 mm Hg), relaxation (UES pressure decreased more than 10 mm Hg less than the baseline trough pressure), or no response. It has been observed that often before and almost always after a swallow-related UES relaxation (because the UES participates in the pharyngoesophageal peristaltic wave), there is an increase in UES tone that has been linked to the preceding relaxation rather than an independent event.[18] We considered UES contraction as a response only if it was not preceded by a UES relaxation response and not followed by UES relaxation within 3 seconds.

Distal and proximal esophageal pressures were measured as an average pressure between 2 adjacent pressure sensors located 3–5 cm above the LES and 3–5 cm below the UES, respectively,[16] and avoided sensors that were affected by cardiovascular pressure markings. The extent of the increase in esophageal intraluminal pressure was recorded as an ordinal variable if (1) proximal and distal esophageal pressure increased more than 3 mm Hg above baseline during perfusion, (2) esophageal pressure increased more than 3 mm Hg above baseline during perfusion only in the distal segment, and (3) esophageal pressure did not increase more than 3 mm Hg in either segment. Esophageal pressure and peak rate of pressure increase (dp/dt) within a 0.1-second window were measured during the perfusion in the proximal and distal esophageal segments as continuous variables.

Esophageal clearing response to distal esophageal perfusion could be classified into 4 categories: (1) tertiary or simultaneous esophageal contraction (>20 mm Hg), (2) secondary peristalsis (>20 mm Hg), (3) primary peristalsis (>20 mm Hg), and (4) no response. LES response to distal esophageal perfusion was classified into 3 types: (1) complete relaxation, defined as equalization of the LES pressure to gastric pressure, (2) partial relax-