



# Functional Changes of the Upper Esophageal Sphincter in Gastroesophageal Reflux

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## Abstract

**Introduction** The upper esophageal sphincter (UES) is a muscular structure located at the transition from the pharynx to the esophagus, with the cricopharyngeal muscle as the most important component. During gastroesophageal reflux, the pressure in the UES elevates, which is apparently a protective mechanism to prevent esophagopharyngeal reflux and airway aspiration. In gastroesophageal reflux disease (GERD), there may be functional changes in the UES.

**Objective** The objective of the present review was to determine UES functional changes in GERD.

**Data Synthesis** In healthy individuals, gastroesophageal reflux causes an increase in the UES pressure. This response of the sphincter is at least partially impaired in patients with GERD. In the disease, the UES has a reduced length and decreased resting pressure. However, other publications found that in chronic gastroesophageal reflux the basal sphincter pressure increase, differences which may be consequent to the measurement method or to disease severity. The UES opening during swallowing has a smaller diameter, and the bolus transit time through the sphincter is longer.

**Conclusion** The UES of patients with GERD does not open as expected and the bolus flow through the sphincter is longer. This behavior may be associated with dysphagia, a frequent complaint in patients with GERD.

## Keywords

- ▶ gastroesophageal reflux
- ▶ upper esophageal sphincter
- ▶ dysphagia
- ▶ heartburn

## Introduction

The upper esophageal sphincter (UES) is a high-pressure region located between the pharynx and the esophagus, resulting from the contraction of the inferior pharyngeal constrictor, the cricopharyngeal muscle and the proximal cervical esophageal muscle.<sup>1</sup> The major functional component of the UES is the cricopharyngeal muscle. This muscle helps maintaining a relatively high UES pressure, which can be either decreased or increased in consequence of different stimuli. The cricopharyngeal muscle is structurally, biochemically, and mechanically distinct from pharyngeal and esophageal muscles.<sup>1</sup> It contains more elastic connective

tissue and sarcolemma than most other striated muscles, and this high degree of elasticity contributes to the opening of the UES.<sup>2</sup>

The UES pressure is not constant. The UES pressure increases in response to slow esophageal distension, pressure on the pharyngeal mucosa, inhalation, awaking, phonation, posture, esophageal secondary peristalsis, stress, increase in intra-abdominal pressure and gastroesophageal reflux; and decreases with anesthesia, sleeping, swallowing, belching, quick esophageal distension, vomiting, exhalation, and in childhood and elderly age.<sup>1–8</sup>

The motor function and sensitivity of the UES are controlled by branches of the vagus and glossopharyngeal

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nerves. Afferent nerves from the UES end in the solitary nucleus, and the main motor nucleus of the sphincter is the nucleus ambiguus.<sup>2</sup> The action of each muscle is directly related to the UES function, which may require either an increased or a reduced pressure in the sphincter.

In gastroesophageal reflux, the UES acts as a barrier to prevent the passage of esophageal refluxate into the pharynx, a situation that increases the risk of aspiration of gastric contents into the airways, causing acute and chronic pulmonary diseases. The UES also avoids the inhaling of air into the esophagus during inspiration. In patients with gastroesophageal reflux disease (GERD), although compensatory changes in the UES functioning may even improve the efficacy of the sphincter in preventing the occurrence of esophago-pharyngeal reflux, these changes may affect its efficiency during swallowing.

Gastroesophageal reflux disease has a prevalence of between 8 and 33% in the world and affects individuals of both genders and all ages.<sup>9</sup> The most common symptoms are heartburn and regurgitation<sup>10</sup> caused by the reflux of gastric content, usually acid, to the esophagus. Also, supraesophageal symptoms may occur. Supraesophageal reflux can cause cough, laryngitis, asthma, dental erosion and voice alteration, and may be associated with pharyngitis, idiopathic pulmonary fibrosis and recurrent otitis.<sup>11</sup>

Normal UES opening during swallowing involves sphincter relaxation, anterior laryngeal traction, and intrabolus pressure<sup>12</sup> and, therefore, functional or anatomical changes of the UES may cause impairment of UES opening and oropharyngeal dysphagia. We reviewed studies that evaluated the UES function in patients with GERD. The small number of studies about the UES in GERD and other diseases a long time ago is a consequence of methodological limitations until about the end of the decade of 1980. When videofluoroscopy and high-resolution manometry was introduced as a possibility for investigation, new knowledge about the pharyngeal-esophageal transition was developed. Investigations performed without the best methodology do not contribute significantly to the knowledge of UES physiology.

## Review of a Particular Subject

A study using modern methodology describes an increase in the UES pressure when gastric contents reach thoracic and cervical segments of the esophagus during gastroesophageal reflux.<sup>13</sup> The pressure response is similar in acid and nonacid liquid reflux, with an increase of  $34 \pm 2$  mm Hg in patients with GERD and of  $27 \pm 6$  mm Hg in patients without GERD.<sup>13</sup> In healthy individuals, intraesophageal infusion of acid or nonacid fluids increase the UES pressure,<sup>6,7</sup> and the pressure also increases with intraesophageal balloon distension.<sup>5</sup> Swallowing a bolus with high levels of acidity does influence UES function, with a prolonged pressure restitution time after swallowing.<sup>14</sup>

In patients with obstructive sleep apnea, the esophageal pressure decreases (median reduction of 4.2 mm Hg) during episodes of apnea, which may favor the occurrence of gastroesophageal reflux. However, increases in the UES and in the lower esophageal sphincter (LES) pressure (medi-

an of 20.1 mm Hg in UES and of 9.6 mm Hg in LES) promote the antireflux barrier against gastroesophageal and esophagopharyngeal refluxes during apnea.<sup>15</sup> This is observed in obstructive sleep apnea patients with or without a diagnosis of GERD, although changes in the UES pressure are less intense in those without reflux disease.

In individuals with chronic GERD, the UES differs functionally from individuals without reflux disease, even at rest (that is, not during reflux episodes). A study evaluating UES motility in patients with GERD reported that almost half of the patients had a short and hypotonic UES, and in those with extraesophageal symptoms, the proportion of hypotonic UES was even higher.<sup>16</sup> In another study, abnormalities in UES function were found in one-third of the patients with gastroesophageal reflux, including patients with laryngopharyngeal reflux and patients with typical GERD. The most common alteration was abnormal UES basal pressure (median of 59.8 mm Hg) in patients with GERD (normal reference value 73.5 mm Hg).<sup>17</sup> In patients with esophagopharyngeal reflux, median UES resting pressure (71 mm Hg versus 126 mm Hg in controls) and median proximal contractile integral (215.5 cm mmHg versus 313.5cm mmHg in controls) were lower than in patients without pharyngeal reflux.<sup>18</sup> On the other hand, there is an investigation with results that the UES may be hypertensive, a self-protective reaction in the esophagus in patients with esophageal chronic acid exposure, a situation that may cause cervical dysphagia, if the sphincter opening diameter decreases.<sup>19</sup>

The UES opening diameter during swallows of 20 mL liquid bolus, evaluated by videofluoroscopy in individuals with hiatal hernia, was lower ( $0.81 \pm 0.24$  cm) than in individuals without hiatal hernia ( $0.93 \pm 0.25$  cm,  $p = 0.02$ ).<sup>20</sup> Cricopharyngeal muscle dysfunction was seen in 78% of patients with hiatal hernia and in 58% of individuals without hiatal hernia in a sample of patients submitted to videofluoroscopy.<sup>20</sup>

Another UES dysfunction in patients with GERD is a slower passage of the swallowed bolus through the UES when compared with healthy controls (duration of flow:  $0.61 \pm 0.02$ s versus  $0.53 \pm 0.02$  second in controls,  $p = 0.03$ ).<sup>21</sup> Similar findings were reported in another study evaluating swallowing of 5mL of liquid bolus (duration of flow:  $0.47 \pm 0.21$  second in patients with GERD and  $0.39 \pm 0.10$  second in healthy controls,  $p = 0.01$ ).<sup>22</sup> A prolonged pharyngeal transit was also observed in patients with GERD ( $0.83 \pm 0.04$  second compared with individuals without GERD ( $0.66 \pm 0.04$  second,  $p = 0.02$ ), with an increased amount of pharyngeal residues in patients with GERD ( $p = 0.03$ ).<sup>21</sup> After swallowing of a 10mL paste bolus, the pharyngeal transit time was  $0.56 \pm 0.31$  second in patients and  $0.47 \pm 0.21$  second in controls ( $p = 0.02$ ).<sup>22</sup> Patients with similar symptoms of GERD but with esophageal endoscopy without lesion and normal quantitative evaluation of the reflux, a situation named functional heartburn, do not have alteration of pharyngeal and UES transit,<sup>23</sup> a demonstration that a longer UES and pharyngeal transit is consequence of gastroesophageal reflux and not of the symptoms.

An incomplete opening of the UES combined with a prolonged UES and pharyngeal transit time may be one of

the causes of dysphagia in GERD patients.<sup>24–26</sup> Reflux disease has been described as the most common disease associated with nonobstructive dysphagia<sup>24</sup> and is reported by 47% of patients with esophagitis.<sup>25</sup> Also, the prevalence of dysphagia was 48% among patients with heartburn and regurgitation, evaluated by patient self-perception.<sup>26</sup> However, there are other possible explanations for dysphagia in patients with GERD, as hypersensitivity and esophageal motility abnormalities.<sup>26</sup> Cricopharyngeal dysfunction is not an important cause of dysphagia in a significant proportion of patients with diseases that cause dysphagia.<sup>27</sup> There are diverse effects of cultural variables on dysphagia,<sup>28</sup> which cause different manifestations in similar situations.

In addition, in patients with GERD, there was a higher frequency (75.8%) of UES pressure increase ( $\geq 10$ mmHg from the baseline) during transient lower esophageal sphincter relaxation compared with healthy controls (17.6%). Decrease in UES pressure during transient lower esophageal sphincter relaxation was observed in 21.2% of GERD patients and in 73.5% of controls.<sup>29</sup>

Electromyographic analysis of the cricopharyngeal muscle in GERD patients did not show differences as compared with findings in healthy volunteers.<sup>30</sup> Also, a study assessing esophageal striated muscle contractions by manometry did not show different results between GERD patients with and without esophagitis.<sup>31</sup>

In healthy individuals, the slow infusion of liquid into the esophageal body causes an increase in the UES pressure,<sup>6,7</sup> which is not observed in patients with GERD with supra-esophageal symptoms, indicating impairment in the UES response.<sup>32</sup> When gastroesophageal reflux is associated with cough, the UES residual pressure during swallowing is higher when compared with controls.<sup>33</sup> The upper esophageal sphincter response to simulated slow and ultraslow reflux events is reduced in elderly individuals, suggesting that the aging process causes impairment of the UES response to gastroesophageal reflux.<sup>34</sup>

In cats, chronic esophageal acid exposure desensitizes the esophageal-UES relaxation and esophageal-UES contractile reflexes.<sup>35</sup> In humans, there is a delay in airway closure relative to the arrival of the bolus at the UES in patients with GERD and dysphagia.<sup>36</sup> There is a reflex interaction between pharynx, esophagus, and airways,<sup>37</sup> which could be impaired in patients with GERD.

Gastroesophageal reflux symptoms, including significant heartburn, may be associated with a new syndrome called retrograde cricopharyngeal dysfunction (R-CPD), which causes inability to belch, abdominal pain, abdominal distention and excessive flatulence.<sup>38,39</sup> The symptoms do not improve with conventional treatment for gastroesophageal reflux with proton pump inhibitors. The best-known treatment so far is botulinum toxin injection into the cricopharyngeal muscle. Whether the R-CPD syndrome is resultant of desensitization of the esophageal-UES relaxation caused by chronic esophageal acid exposure<sup>39</sup> is a matter for future investigations. Gas presence in the esophageal body should decrease the UES pressure and cause a belch.<sup>40</sup>

**Table 1** Summary of results of investigations about upper esophageal sphincter in gastroesophageal reflux

Reference	UES alteration
Torricco et al. <sup>13</sup>	Increase pressure during reflux
Kuribayashi et al. <sup>15</sup>	Increase pressure during reflux
Bognár et al. <sup>19</sup>	Hypertensive sphincter
Kim et al. <sup>29</sup>	Increase UES pressure during transient LES relaxation
Babaei et al. <sup>32</sup>	No increase in pressure during slow infusion of liquid into esophageal body
Nadaletto et al. <sup>16</sup>	Short and hypotonic sphincter
Benjamin et al. <sup>17</sup>	Decreased pressure
Passaretti et al. <sup>18</sup>	Decreased pressure in patients with pharyngeal reflux
Mendell et al. <sup>21</sup>	Slower transit through the sphincter
Cassiani et al. <sup>22</sup>	Slower transit through the sphincter
Alkan et al. <sup>30</sup>	No alteration of cricopharyngeal EMG
Bastian et al. <sup>39</sup>	Inability to belch

Abbreviations: EMG, electromyography; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

A summary of results about UES evaluation in GERD is in **Table 1**.

## Discussion

Gastroesophageal reflux disease symptoms have an incidence range that is different among countries. It is high in North America, Australia, Oceania, and Northern Europe; medium in Western Asia, Southern Asia, and South America; low in Eastern Asia, and Southern Europe.<sup>41</sup> The most frequent symptoms of the disease are heartburn and regurgitation, with dysphagia considered an alarm symptom. Common causes of dysphagia in GERD are peptic stricture and severe inflammation; however, cancer and nonobstructive dysphagia are possibilities.<sup>26,42</sup> When patients have progressive dysphagia and/or troublesome dysphagia, endoscopy is mandatory.

The UES is composed of striated muscle and responds to stimulus, increasing or decreasing its pressure. Dysphagia in GERD may be perceived in a situation of partial UES opening and slower bolus flow during swallowing;<sup>19,21,22</sup> however, it is usually mild and may improve with clinical or surgical treatment of the disease.<sup>43</sup> Swallows of a larger bolus volume cause an increase in UES opening duration and in UES diameter,<sup>12,44</sup> with is restricted in patients with GERD. The increase in UES diameter caused by increase in bolus volume is associated with increase in the anterior maximal hyoid and laryngeal movements,<sup>12,44</sup> which are adaptations to bolus

volume that may be compromised in patients with GERD, with impairment of the UES opening diameter.<sup>20</sup>

It is proposed that GERD should be considered a family of syndromes with different pathophysiology, which include erosive GERD, nonerosive GERD, hypersensitive esophagus and functional heartburn,<sup>45</sup> not always as a consequence of increased gastroesophageal reflux. The UES changes in patients with reflux symptoms is likely to be a consequence of the esophageal exposition to acidic reflux, and perhaps nonacidic reflux, but not of heartburn complaint.

The UES opening restriction can also increase the possibility of partial aspiration of the swallowed bolus into the airway, a situation that needs further investigation. The possibility of airway penetration in the disease is increased.<sup>21</sup>

## Final Comments

The UES of patients with GERD may not open as expected, which is associated with slower pharyngeal and UES transit. This behavior should aim to avoid the occurrence of esophageal-pharyngeal reflux.

### Conflicts of Interest

The author has no conflicts of interest to declare. Roberto O. Dantas is a member of the Board of Directors of the International Dysphagia Diet Standardization Initiative (IDDSI).

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