The role of this paper is to present the current concepts in anatomy and etiopathogenesis of pharyngeal diverticula. Precise anatomical considerations highly emphasizing the weak anatomic areas which predispose the pouch formation are discussed. Focus exposed in details will also be given upon the structural and functional characteristics of the upper esophageal sphincter as well as to its physiological states, architecture and dynamic functions. A brief review of historical and current perspectives regarding the origin of pharyngeal diverticula has also been given. Special attention is given to the abnormal cricopharyngeal function in patients with pharyngeal pouches in the terms of altered UES compliance, importance of gastroesophageal reflux and histopathologic changes of cricopharyngeal muscle.

Key words: Upper esophageal sphincter, Zenker diverticula, etiopathogenesis

ANATOMICAL AND TOPOGRAPHICAL CONSIDERATIONS

The UES is defined as an area of high intraluminal pressure that forms a barrier between the pharynx and the cervical esophagus. This definition implies three responses: tone generation, phasic response activity, and sphincter opening. The UES relaxes and opens during swallowing, allowing the passage of food and liquids into the esophagus, while at the same time provides a barrier against its retrograde flow. By doing so, he represents an important protective function preventing aspiration of acidic gastric content into the respiratory tract on one side, and on the other entry of air into the esophagus. The UES also permits, by its physiologic relaxation, retrograde flow of material during belching, and vomiting.

Anatomically observed, the pharyngoesophageal junction or area encompassing the tone generation function of the UES is sometimes referred to as the pharyngoesophageal segment or sphincter (PES) as well as upper esophageal high-pressure zone (UEHPZ). Although the physiologic concepts of UES are mostly clear, the anatomic components of these concepts are not. By the structural anatomy standpoint, the pharyngoesophageal junction or UES represents a musculocartilaginous structure composed of the posterior surface of the thyroid and cricoid cartilage, the hyoid bone, and three muscles: inferior pharyngeal constrictor (IPC), cricopharyngeus (CP) and cranial or cervical esophagus (CE).1,2,3,4 (Figure 1). CP together with the cranial part of the cervical esophagus constitutes the lower third of the entire pharyngoesophageal high-pressure zone, while the IPC muscle accounts for the remaining upper two thirds of the UES.4

The physiologic function of the UES is mainly based on the sole activity of cricopharyngeal muscle. The CP is a striated muscle attached to the cricoid cartilage that is in average 1.9 cm in length in males and 1.6 cm in females.1,3 CP forms a c-shaped muscular band that produces maximum tension in anteroposterior rather than lat-
eral directions. The CP is suspended between the cricoid processes, surrounds the narrowest part of pharynx, and extends caudally where it blends with the circular muscle of the cervical esophagus. Two sets of CP muscle fibers have been identified: the horizontally oriented fibers (pars fundiformis), which occlude the esophageal introitus, and an oblique band of fibers (pars obliqua), which are responsible for propulsion of the bolus. Both types of fibers of CP extend from the lateral aspect of the cricoid cartilage to the posterior midline raphe, where they blend superiorly with the IPC.5 The horizontal fibers of the CP encircle the upper esophagus, forming a sling between the two sides of the cricoid cartilage.6

The inferior pharyngeal constrictor muscle extends from the oblique line of the thyroid cartilage to insert into the posterior midline pharyngeal raphe, a fibrous band extending from the base of the skull, to which all of the bands of constrictor muscles are attached. Unlike the IPC, the pars fundiformis of the CP has no median raphe.3,4 Killian’s triangle, also known as dehiscence, through which pharyngoesophageal Zenker diverticula occur, represents an anatomical triangular area of sparse musculature of the IPC, bordered superiorly by the firm oblique fibers of the IPC and inferiorly by the horizontal fibers of the CP, mostly lying in the posterior midline just above the cricopharyngeal sling and below the pharyngeal raphe.7,8,9,10

The cervical esophagus begins at the lower border of the cricoid cartilage and contains predominantly striated muscle fibers, but occasionally smooth fibers are found in the center of the muscle. The muscle fibers are arranged in two layers: the external layer containing longitudinal, and the internal layer containing circular or transversely arranged fibers. The inner circular layer blends superiorly with the cricopharyngeus. The longitudinal layer, however, diverges at its upper end approximately one to two cm from the CP, forming two bands that swing laterally and anteriorly around the esophagus to attach to a common tendon behind the cricoid cartilage.

Therefore, the posterior esophageal wall between these two diverging bands is the single circular layer of muscular fibers. This forms the second potentially weak area, known as Laimer’s triangle or the Laimer-Haeckerman area.11 The external longitudinal layer courses down the length of the entire esophagus. At its distal end the longitudinal fibers become more oblique and end along the anterior and posterior gastric wall.12 The internal circular layer of the esophageal muscle originates at the level of cricoid cartilage and in descending forms incomplete circles down to the esophagogastric junction.

Another space of weakness at the pharyngoesophageal junction is the Killian-Jamieson area. This is a muscular gap in the posterolateral wall located between the oblique and transverse fibers of the cricopharyngeal muscle. Some authors describe this area as the space of the cervical esophagus inferior to the cricopharyngeus and lateral to the longitudinal muscle of the esophagus just below its insertion on the posterior lamina of the cricoid cartilage. This area is bounded superiorly by the lowest crico-
In the pharyngolaryngeal area a typical lateral pharyngeal or pharyngolaryngeal pouches also can be found. They originate at the weak point of the thyrohyoid membrane and are mainly considered congenital in origin. (Figure 2)

NEUROMUSCULAR COMPLEXITY AND THE BIO-PHYSICS OF THE UES

Despite decades of sophisticated studies, there is still a controversy over precisely which muscles comprise the predominant function of UES. The location and structure of the CP muscle appears well suited to sphincter function, and conventional wisdom holds that the CP is the major muscle of the UES. Several studies have investigated the separate role of CP, IPC and the cervical esophagus in the unique functioning of the UES.\textsuperscript{14,15} In rest, both IPC and CP muscle contribute equally, expressing the similar neuromuscular activity which fluctuates in association with changes in the intraluminal pressure.\textsuperscript{16,17}

Some of the intrinsic pressure of the UES is possibly contributed by the infracricoid esophagus, but continuous activity has not been recorded.\textsuperscript{15,16,17} UES contraction and relaxation during retching and vomiting occur by the simultaneous action of the CP, IPC, and proximal cervical esophagus.\textsuperscript{16,18} During swallowing and belching, CP shows the most prominent drop in pressure and active relaxation\textsuperscript{15,18}, while on the other hand CP and IPC both show active contractility during coughing and sneezing\textsuperscript{19}. UES contraction in response to esophageal or pharyngeal distension occurs mainly with the action of CP.\textsuperscript{15}

Taking all this facts in account, of all UES muscles only the cricopharyngeal functions is present in all physiological states. CP is composed of striated muscle of small average diameter fibers (25-35 m) which are not oriented in a parallel fashion.\textsuperscript{20,21,22} These fibers are of predominantly slow twitch (type I), an oxidative skeletal muscle type important for maintenance of basal tonicity.\textsuperscript{23,24,25} The presence of some fast twitch fibres (type II) allows rapid contraction during swallowing, belching and vomiting.\textsuperscript{19-22}

Compared with other striated muscles, the CP has abundant (about 40\%) connective tissue (dominated by elastic elements) and larger cell membrane of a muscle cell or sarcolemma (the CP muscle fibers are smaller than most striated muscle fibers and therefore have more sarcolemma).\textsuperscript{24,25,26,27} These structural characteristics as well as the network arrangement of muscle fibers and connective tissue could account for the passive elastic behavior.\textsuperscript{21}

Such a histological specificity results in characteristics similar to Starling’s law of cardiac muscle where the tension increases as the muscle is distended. The maximal tension in CP is generated at 1.7 times its basal length.\textsuperscript{15} This elasticity of CP serves several functions:

a) CP distends as a bolus is pushed through the sphincter without the need for active relaxation,\textsuperscript{3}
b) rapid closure is aided after passage of material through the UES and basal tone is generated at all diameters without additional neural input.\textsuperscript{5,15,24,25,26,27}

TheCP receives innervation from the pharyngeal plexus, which is supplied by three major nerves: vagus nerve branches including the pharyngeal branch of the vagus nerve (also referred to as the pharyngoesophageal nerve (PEN), superior laryngeal nerve (SLN), and recurrent laryngeal nerve (RLN)), the glossopharyngeal nerve (GPN) and sympathetic nerve fibers from the superior cervical ganglion. Although many nerves appear to project to the CP, the PEN provides the major motor innervation of the CP.\textsuperscript{28,29} The motor innervation of the IPC is supplied primarily by the pharyngeal branch of the vagus nerve through the pharyngeal plexus.\textsuperscript{30}
Many studies have attempted to trace nerve fibers through the pharyngeal plexus to the IPC, but because this innervation is through a plexus of interconnecting nerves, it is not possible to definitively determine which branch exactly supplies the IPC. The entire IPC muscle has a single vertical band of motor end plates that corresponds to the location of the pharyngeal plexus (Figure 3). On the other hand, the cervical esophagus is mainly innervated by the RLN. The terminal branches travel around the esophagus in a circular fashion and appear to cross the midline both anteriorly and posteriorly.

ARCHITECTURE AND DYNAMIC FUNCTION OF THE UES

The upper esophageal sphincter is usually closed by resting muscle tone and opened during swallowing by relaxation of muscle fibers together with cephalic displacement of the larynx, creating a negative pressure. The closing or resting pressure of the UES varies with the circumstances under which the measurements are made. The pressure profile of the UES shows axial asymmetry with a sharp increase and gradual decrease in pressure moving inferiorly through this zone, as well as marked radial asymmetry. These intrasphincteric pressure characteristics have been best described by Welch and colleagues who constructed a three-dimensional pressure profile of the UES.

The pressure applied in the antero-posterior plane is three times greater than at the lateral plane, with a dislocation of the peak pressures along the anterior and the posterior aspects. Upper esophageal high pressure zone measures between 2.5 and 4.5 cm in length, and the peak pressure manifest itself below the upper border of the high pressure zone, one cm anteriorly and two cm posteriorly. Resting pressures in normal subjects have been reported to be with high variations, between 35 and 200 mmHg. At the level of CP muscle this pressure is measured to be in average 55-75 mmHg in anteroposterior direction and 20-30 mmHg transversely.

During deglutition the UES converts rapidly from a closed state to an open state to allow passage of the swallowed bolus into the esophagus. During this opening the lumen assumes an oval cross section, after which it closes as the bolus leaves the pharynx. Relaxation and opening of the UES occur during deglutition, rumination, vomiting, and belching. Following swallow initiation, approximately 0.2 to 0.3 seconds prior to the onset of UES opening, transient inhibition of vagal input to the muscular components of the UES leads to a loss of active tension in the sphincter region.

On swallowing, the UES high-pressure zone falls to resting atmospheric pressure and remains open to accommodate bolus transport though the sphincter area. This relaxation is brought about by cessation of vagal nerve stimulation and by upward displacement and elevation of the larynx by the suprahypoid muscles (geniohyoid, mylohyoid, and thyrohyoid) which pull the UES aborally. Indeed, activation of these muscles can decrease intraluminal pressure within the UES even when the tone is not inhibited. Because of its attachment to the larynx, which moves with deglutition, the UES moves upward 2 to 2.5 cm.

In addition, the pressure applied by the onrushing bolus can push open the lumen of the UES. Therefore, it is possible for the UES to relax without opening and open without relaxing.

Full sphincter relaxation is observed in the period of 0.5 to 1.2 seconds and with passage of the hypopharyngeal contraction the sphincter closes with a contraction that creates a pressure that is often twice as high as the resting pressure of the UES itself, called "postrelaxation contraction". Based on normal data from our motility laboratory, a deglutitive UES nadir pressure less than 10 mmHg, when measured by a sleeve sensor and during a "dry swallow", is considered a complete UES relaxation. (Figure 5). Subsequent to these phenomena, the degree of actual UES relaxation is usually 20 OM Skrobić et al. ACI Vol. LVI.
opening is determined by a balance among three forces: UES muscle tension, intrabolus pressure, and external traction forces on the cricoid cartilage.

It has been documented that manometric tests failed to detect any abnormality in even 40 per cent of patients with Zenker’s diverticulum. There are several reasons why manometric testing may fail to detect pharyngoesophageal function abnormalities in Zenker’s diverticulum: a) CP, which roughly corresponds to the UES, generates asymmetric pressures with a considerable variability in each of the axes, b) contractions of the pharyngeal striated muscle cause pressure events to be much faster and greater in amplitude than in the distal esophagus, c) the UES is extremely mobile and moves proximally nearly 1 cm during swallowing, thus causing the recording site to “drop out” if it is placed in the central part of the UES.

This “dropping out” of the recording site may explain the apparently “normal” relaxation observed by previous researchers. Dent proposed and Kahrilas adapted the manometric sleeve concept which is effective in UES pressure measurements despite the movement during the deglutition. However, this method did not provide satisfactory measurements concerning the pharyngeal contraction and UES relaxation. Castell et al proposed positioning the recording sensor above the high-pressure zone of the sphincter for that purpose, thereby allowing the opened sphincter in its upward excursion, to be studied.

**CRICOPHARYNGEAL DISFUNCTION AND THE ORIGINS OF PHARYNGEAL DIVERTICULA**

Upper esophageal sphincter relaxation, indeed the entire repertoire of pharyngeal and cricopharyngeal motor events during deglutition, originates in the medullary swallow center. Hence, it is not surprising that the majority of identifiable disorders underlying failed UES relaxation and manifesting as a pharyngeal or cervical dysphagia most commonly arises from neurogenic or myogenic diseases. In these diseases dysphagia is frequently a part of wider neurologic syndrome, making it necessary for the clinician to consider a wide range of diagnostic possibilities and appropriate investigations. In this paper our main objective was to present possible pathophysiologic pathways in origin of pharyngeal and pharyngoesophageal diverticula, or intrinsic cricopharyngeal muscle disfunction leading to cervical dysphagia.

Pharyngeal diverticula as already mentioned may be posterior, posterolateral, or lateral, but the most commonly encountered type is the posterior pulsion or Zenker’s diverticulum (ZD). After more than a century of debate and investigation there is no general consensus regarding the exact etiology of ZD. For years most widely accepted mechanism of the ZD development has been a functional disturbance of the pharyngoesophageal segment, mainly a combination of increased resting pressure of the sphincter, lack of complete relaxation, and in particular, incoordination of the hypopharynx and upper esophageal sphincter. (Figure 6)

Westrin et al suggested that two abnormalities predispose formation of the posterior pharyngeal diverticulum: anatomic weakness of the posterior pharyngeal musculature adjacent to UES and/or muscular dysfunction of the UES. We previously described anatomical configuration of UES, and emphasized the potentially weak areas. But the Killians triangle as a congenital weakness can not itself explain the formation of the diverticula. ZD usually occur in the individuals aging between 60 and 70 years, and during the decades as the normal part of aging, swallowing mechanism can be altered.

Age related changes include: increased hypopharyngeal pressure, decreased number of cells in the Auerbach’s plexus, need for multiple swallows to effectively clear the oral cavity and diminished coupling between the oral and pharyngeal phase of swallowing. It has been postulated that excessive contraction of the pharyngeal and CP muscles creates the necessary conditions for herniation of the esophageal mucosa through the weak areas of pharyngoesophageal junction. This kind of possible etiopathogenesis of the ZD has been called the "neuromuscular dysfunction theory".

In his work concerning the origins of ZD Peters using specialized cricopharyngeal manometric recordings, postulated that the pathophysiology of pharyngeal pouches involves "altered compliance of the cricopharyngeal muscle" detected as impaired sphincter opening or raised intrabolus pressure. Hypopharyngeal intrabolus pressure is the low-pressure domain (2-10 mmHg) within the bolus itself, which is registered before the onset of the major pressure upstroke caused by the advancing hypopharyngeal contraction (100 mmHg).

It can be appreciated that intrabolus pressure will vary as a function of the resistance to bolus flow offered by the UES, and that the major determinant of such resistance is sphincter diameter. In ZD, combined radiographic and manometric studies have confirmed normal pharyngospincteric coordination, normal resting UES tone, and complete UES relaxation during the swallow. Those studies demonstrated that opening of the UES was restricted, and as a result that hypopharyngeal intrabolus pressure had increased. Hence, as originally suggested by Zenker himself, diverticulum formation is due to a poorly compliant but normally relaxing UES that cannot fully distend during the process of sphincter opening. Shaw et al supported these finding of poor UES compliance and added that hypopharyngeal intrabolus pressure is a useful indicator of upper sphincter compliance which normalizes after surgery.

Why is UES opening restricted in patients with ZD? Histopathologic studies of the CP and IPC muscles, retrieved at the time of cricopharyngeal myotomy in patients with ZD, showed myopathic features including muscle fiber degeneration and necrosis, phagocytosis, and increased fibroadipose tissue replacement confined to the CP muscle. These morphologic changes in the CP muscle do influence the contractile and elastic properties of the muscle and probably account for its restricted opening.
When compared with the normal CP muscles, the muscles in patients with ZD demonstrates histologic and biochemical abnormalities consistent with fiber dropout (due to necrosis, as evidenced by scattered degenerative fibers), greater fiber size variability, and marked increase in fibroadipose tissue replacement leading to decreased muscle-connective tissue ratio. Fatty replacement of muscle fibers and increased type I muscle fibers, which are highly oxidative slow twitch and are responsible for tonic contraction, have also been found in the CP muscle of patients with ZD.

Another issue that has been debated for years is the role of pathologic gastroesophageal reflux in etiology of crico-pharyngeal spasm and formation of ZD. Association between GERD and ZD was also reported in numerous studies and it counted 1494-8. The higher incidence of GER among the patients with ZD was also reported in numerous studies and it counted from 22% to up to 95%. Nevertheless, clear connection between GERD and hiatal hernia on one side and ZD on the other, has not been firmly established, although higher incidence of GER and hiatal hernia among the patients with ZD. Even though that UES is not just one muscle, but is composed of sets anatomically and physiologically different muscles, the primary component that governs all the functions of the UES is the CP. The primary unique function of the CP is to prevent esophageal air insufflation during negative intrathoracic pressure and the esophagopharyngeal reflux. The pressure of the UES decreased after the antireflux surgery. The problem with this study was unreliable manometric equipment and the difficulties with technique of the UES resting pressure measurement, which we previously described.

Results of Simleys study were compromised by later manometric studies of UES in patients with ZD, using the constant perfusion manometric device.52 No significant elevation of CP muscle resting pressure was found in patients with reflux esophagitis or symptoms of GERD.

The higher incidence of GER among the patients with ZD was also reported in numerous studies and it counted from 22% to up to 95%. These studies are difficult to compare because there is no standardization in GERD diagnosis. In addition, pharyngeal reflux and its manifestations occur in only 20 - 50% of patients with typical GERD symptoms. Hiatal hernia incidence has also been reported to be increased in patients with ZD, and Feussner reported it to be up to 77% in his series.58

Nevertheless, clear connection between GERD and hiatal hernia on one side and ZD on the other, has not been firmly established, although higher incidence of GER and hiatal hernia is noted in patients with ZD opposed to controls and normal population. Another reasonable question is how reflux can provoke the crico-pharyngeal muscle spasm, or increased intrabolus pressure. Possible explanation could be inflammation-induced sclerosis of the CP muscle which is causing the failure of adequate distension during swallowing. Decreased muscle compliance of the CP requires increased intrabolus pressures to maintain flow of swallowed materials, and therefore it is possible that reflux induces the histological changes of the CP muscle.

Even though that UES is not just one muscle, but is composed of sets anatomically and physiologically different muscles, the primary component that governs all the functions of the UES is the CP. The primary unique function of the CP is to prevent esophageal air insufflation during negative intrathoracic pressure and the esophagopharyngeal reflux. In the past, most research investigations have concentrated their efforts on focusing on the pathophysiology of the UES in the spectrum of pharyngoesophageal diverticula. In the future studies, the role not only of the CP or pharyngoesophageal junction has to be investigated, and a special emphasis of the whole foregut must be taken into account. By making this kind of approach to the several century old problems, we shall increase our knowledge on the subject of wider spectrum of entities in the possible origins of pharyngeal pouches.

**SUMMARY**

**SAVREMENI KONCEPT ANATOMIJE I PATOFIZIOLOGIJE FARINGEALNIH DIVERTIKULUMA**

Cilj ovog rada je da se prikažu osnovi anatomije i patofizijologije gornjeg ezofagealnog sfinktera (GES) u cilju razmatranja etiologije faringealnih divertikula. Rad počinje sa detaljnim anatomskim prikazom anatomiјe GES-a i posebnim osvrtom na anatomski slabe regije kao predisponirajuća mesta za nastanak divertikula. Nakon toga bice prikazane strukturne i funkcionalne karakteristike mišića koji sačinjavaju GES, a potom i fiziologija gornjeg ezofagealnog sfinktera, njegova arhitektonika i dinamička funkcija. Iznosimo pregled istorijskiх i aktuelnih koncepta etiopatogeneze divertikula. Ukazujemo na značaj poremećene krikofaringealne funkcije u smislu oslabljene komplijisanе ГЕS-a, kao i histopatološkiх promena krikofaringealnog mišićа. Poredаčen je i značajpatološkog gastroezofagealnog refluksа u genezi diver- tikuluma kroz pregled literature koja se odnosi na ovu problematiku.

**Ključne reči:** gornji esofagealni sfinkter, Zenkerov divertikulum, etiopatogeneza

**BIBLIOGRAPHY**


