Esophagus and Its Function Related to Gastro-esophageal Reflux

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ABSTRACT

The main function of the esophagus is to transport food from the mouth into stomach. Anatomical structures, innervations and blood supplies are needed in order to transport the food into stomach. Mastication stimulates the parasympathetic nerves that regulate salivary, gastric and pancreatic secretion. Saliva secretion stimulates swallowing and increases primary esophageal peristalsis, helps in clearing the esophagus from refluxed material. Swallowing induces peristaltic of esophagus that propulses a solid bolus down the esophagus into the stomach.

Innervations are important for esophagus to do its function. One of the most important is coordination between the various reflexes. Delayed clearance of acid from the esophageal and decreased pressure of the lower sphincter esophagus (LES) are the major mechanisms involved in the development of esophagitis. The resistance of the mucosa to the noxious effect of the refluxed material (acid, pepsin, chymotrypsin and trypsin, bile, etc.) is different from person to person. The LES pressure is a defense mechanisms to prevent gastro-esophageal reflux disease (GERD). The LES pressure decreases postprandially. The frequency of postprandinal GER is related to the meal size. Gastric bolus feeding is related to greater intragastric pressure causes more of transient LES relaxations. Osmolality and volume of the feeding slow gastric emptying and incrase postprandial GER. The occurrence of GERD is associated with whether or not the preventive factors are functioning. Other preventive factors for GERD are esophageal peristalsis, secretion and mucosal resistance, gravity and position, the LES tone and angle of his. Patient with GERD should be searched for any disturbances on those factors.

Keywords: *gastroesophageal reflux diseases, lower esophageal sphincter, esophagitis, peristaltic*

ABSTRAK

Fungsi utama dari esofagus adalah menghantarkan makanan dari mulut ke dalam lambung. Struktur anatomi, persarafan dan perdarahan diperlukan dalam proses menghantarkan makanan ke dalam lambung. Mengunyah dapat menstimulasi saraf parasimpatik yang mengatur sekresi saliva, lambung dan pankreas. Sekresi saliva menstimulasi proses menelan dan meningkatkan peristalsis esofagus primer yang membantu membersihkan esofagus dari materi refluks. Proses menelan menginduksi peristalsis esofagus yang mendorong bolus makanan padat dari esofagus ke dalam lambung.

Persyarafan merupakan hal penting bagi esofagus dalam menjalankan fungsinya dan salah satu yang paling penting adalah koordinasi dari berbagai jenis refleks. Terganggunya bersihan asam dari esofagus dan penurunan tekanan sfingter esofagus bawah (SEB) merupakan mekanisme utama yang berpengaruh terhadap terjadinya esofagitis. Resistensi mukosa terhadap efek toksik dari materi refluks (asam, pepsin, kimotripsin dan tripsin, empedu dan lain lain) berbeda antara satu individu dengan lainnya. Tekanan sfingter esofagus bawah (SEB) merupakan mekanisme pertahanan untuk mencegah terjadinya penyakit refluks gastroesofagus (PRGE). Tekanan SEB menurun paska makan. Frekuensi refluks gastroesofagus (RGE) paska makan berhubungan dengan porsi makan. Pemberian bolus makanan ke dalam lambung berhubungan dengan peningkatan tekanan intragaster

sehingga menyebabkan peningkatan frekuensi relaksasi sfingter esofagus bawah sementara. Osmolalitas dan volume makan memperlambat pengosongan lambung dan meningkatkan RGE pasca makan. Terjadinya PRGE diasosiasikan dengan berfungsi atau tidak faktor preventifnya. Faktor preventif PRGE lainnya adalah peristalsis esofagus, resistensi dan sekresi mukosa, gravitasi dan posisi, tonus SEB dan angle of his. Pada pasien dengan PRGE gangguan apapun pada faktor preventif tersebut harus dicari.

Kata kunci: *penyakit refluks gastroesofagus, sfingter esofagus bawah, esofagitis, peristaltik*

INTRODUCTION

The main function of the esophagus is transport food from the mouth into stomach. Although it looks simple but its function involves several complex mechanisms such as mastication and swallowing processes, lubrication food material by saliva, secretions of the esophagus, and esophageal peristalsis which delivers food and prevention of retrograde transport from the stomach to the mouth.[1] Anatomical structures, innervations and blood supplies are needed in order to transport the food into stomach. The upper esophageal sphincter (UES) and the lower esophageal sphincter (LES) are the important anatomical structures in the protection against gastro-esophageal reflux (GER). There are 4 physiologic anatomic constriction areas, the first at the level of crycopharyngeal sphincter, the second at the level arch of aorta crosses anteriorly, the third at the level left main stem bronchus crosses anteriorly and the fourth at the lower esophageal sphincter. These physiologic areas serve as a barrier from the reflux and foreign body.[2,3] Blood supplies are needed to maintain their metabolism and function. Innervations of the esophagus induced peristalsis wave which transport food into the esophagus.[1]

Impaired differentiation of esophagus during embryology process may cause disruption to the anatomical structures that help prevent gastro-esophageal reflux disease (GERD). The protection mechanism of bicarbonate-secreting cells may not present, muscles and innervations that important in the process of peristalsis and clear the reflux material may also be disrupted.[3] Seeing these, it is important to understand the formation and function of the esophagus respect to GERD

MASTICATION AND SWALLOWING

The major function of mastication is to prepare food mechanically for transport and to start digestion. Mastication stimulates the parasympathetic nerves that regulate salivary, gastric and pancreatic secretion. The larger the volume of saliva, the more the food is lubricate, and the easier esophageal transport becomes. Grinding the food to very fine particulate prevent excoriation and increases the ease of emptying food from stomach into small intestine. The easier the emptying, the more of transient LES relaxations (TLESRs) frequency is reduce.[4]

Swallowing is initiated when the most sensitive tactile areas of the posterior mouth and pharynx is stimulated. Following a swallow, the UES relaxes, respiration is inhibited and the glottis closes. The muscles of the esophagus relax and respiration resumes as the UES contracts to separate the bolus from the pharynx and the airway. The important reduction of swallowing rate during sleep may contribute to a delayed esophageal clearance of nocturnal reflux episodes.[5] GER stimulates salivary secretion, which become mainly effective in prolonged episodes of GER. Saliva secretion stimulates swallowing and increases primary esophageal peristalsis, and it helps in clearing the esophagus from refluxed material by its volume.[4]

Dysphagia, or difficulty swallowing, occurs in association with oral and esophageal anatomic abnormalities, neurologic and motor disorders, oral and esophageal inflammatory diseases and psychological stressors or disorders. Of the mucosal disorders, eosinophilic esophagitis is increasingly recognized as being a more common cause of dysphagia or odynophagia than GERD, although this finding is not consistently reported in all geographic regions. Odynophagia, or pain caused by swallowing, must be distinguished from heartburn (substernal pain caused by esophageal acid exposure) and dysphagia. Although odynophagia may be a symptom of peptic esophagitis, it is more often associated with other conditions such as oro-pharyngeal inflammation, esophageal ulcer, eosinophilic esophagitis, infectious esophagitis and esophageal motor disorders.[5]

Although GERD is not a prevalent cause of difficulty of swallowing or pain with swallowing, an evaluation including barium upper gastrointestinal series and possibly upper endoscopy should be considered if physical examination and history do not reveal a cause. Therapy with acid suppression without prior evaluation is not recommended. In the infant with feeding refusal, acid suppression without prior diagnostic evaluation is not recommended.[5]

ESOPHAGEAL PERISTALTIC

The pressure of the UES increases when ingested material or acid refluxes in the esophagus.[7] Swallowing induces primary peristaltic of esophagus that propulses a solid bolus down the esophagus into the stomach. The pressure of the UES disappears during sleep, but increases in stress situations and during straining. The pressure of UES also disappears when there is air in the esophagus, as in belching.[2]

Primary peristaltic is simply a continuation of peristaltic wave that begins in pharynx and spreads into esophagus. Food swallowed in the upright position is usually transmitted faster than the peristaltic wave itself, because of the additional of gravitational force. If the primary peristaltic wave fails to move all the food into stomach, then secondary peristaltic wave begins as the result from the distension of esophagus.[8,9] This wave continue until all the food emptied into the stomach. This wave is initiated partly by intrinsic neural circuit in myenteric nervous system and partly by reflexes that begin in pharynx and transmitted upward through vagal afferent fibers to medulla and back again to esophagus via glossopharyngeal and vagal efferent nerve fiber.[10,11]

Secondary peristalsis contributes to esophageal clearance of remnants of the refluxed material that were not cleared by a primary peristaltic wave. The UES opens and closes at each swallow, while the LES opens when the first peristaltic wave enters the sphincter, and only closes when the last contraction has passed by. Secondary peristalsis is also caused by GER. There is also tertiary peristaltic waves which occurs spontaneously without any relation to swallows or reflux. Peristaltic wave disturbance will affect the clearance of reflux material. When this process occurs repeatedly, it can damage the esophageal mucosa.[12]

ESOPHAGEAL INNERVATION

Medullary circuits comprising premotor neurons of the nucleus tractus solitarii are instrinsically capable of generating rhythmic esophageal motor output, but are subject to a powerful modulation by peripheral sensory feedback. The role of the vagal nerve endings is still poorly understood. The thoracic esophagus is innervated by vagus plexus from vagus trunk in the chest.[2,3,13] The physiologic link between GERD and pulmonary disease has been studied in chronic cough and asthma. The tracheobronchial tree and the esophagus have common embryonic foregut origins and share autonomic innervation through the vagus nerve.[14] It can be speculated that GER increases the irritability of the vagal nerve endings in the esophagus, and that as a result these nerve endings hyper-react together with the nerve endings in the airways. When there are disturbances then it may affect peristalsis and the clearance of the esophagus.[4]

ESOPHAGEAL RECEPTORS

It is assumed that different kind of receptors are present in the esophagus: mechanical, chemical, temperature and osmolarity sensitive receptors, although they have not all been convincingly anatomically identified.[15] Every individual has the opportunity to feel pyrosis or heartburn as a symptom of acid reflux. When very hot or ice-cold substances are swallowed, these differences in temperatures are felt by the individual. When very large substances are swallowed or when an intra-esophageal balloon is inflated, the increase in volume is felt by the test person. Esophageal distention elicits spike activity in single vagal and splanchnic afferent fibers.[16] Nociceptive responses vary between individuals. In pathologic conditions, receptors become nociceptive and have increased sensitivity, thus responding with the sensation of pain to (physiologic) stimuli that normally do not cause pain.[17] Esophageal distention and acid perfusion induces spatially and temporally distinct cortical activation.[18] In Barrett's esophagus, mucosal sensitivity is decreased. The nociceptors inform the patient about the existence of tissue damage. Repetitive stimuli or a very strong stimulus can sensitize fiber afferent neurons to respond to non-noxious stimuli, as very painful.[19] This may result in the fact that a relative small esophageal distention as occurring in belching, minimal regurgitation, or even the passage of a swallowed food bolus, are experienced as very painful. The sensation of pain is transported to the brain via calcitonin gene related peptide (CCRP) and substance P. Substance P has been best studied: it causes smooth muscle contractions, vasodilatation and thus increased mucosal permeability. Substance P is released when there is tissue damage, thus when there is esophagitis, inducing a vicious circle. Extensive tissue damage will increase substance P, which results in side effects of reflux material will be higher.[19]

Substance P causes also histamine release from the mast cells in the alveoli, and thus contributes to bronchospasm. The latter suggests the complexity of the relation between GER/GERD and chronic respiratory

disease.[20] Reflux may be causing respiratory symptoms through a direct relation by (micro-) aspiration. Many patients with chronic cough have gastrohypopharyngeal reflux.[21] Although simply observing the presence of lipid-laden alveolar macrophages is likely to be nonspecific, it has been suggested that quantification would be a useful marker of silent aspiration.[22,23] A high number of lipid-laden macrophages is likely to be related to aspiration, but that a low number does not rule out the hypothesis. An elevated index of lipid-laden macrophages can be found in a variety of pulmonary diseases in which there is no clinical evidence of aspiration and is therefore unlikely to be a specific marker for silent pulmonary aspiration.[24]

Data are lacking and thus needed on the diagnostic accuracy, sensitivity and specificity of the detection and quantification of other substances in tracheal aspirates, such as lactose, pepsin, intrinsic factor, and others. The reverse may as well be happening: respiratory difficulties cause greater respiratory breathing efforts and thus more pronounced negative intrathoracic pressures, and thus respiratory symptoms may provoke GER. However, the incidence of a direct temporal relation between reflux and cough episodes is relatively low,[21] Or the relation may be neurogenic.[25] The visceral hyperalgesia will result in a disordered motility, causing more reflux. This all suggests the following hypothesis: in some patients, acid GERD may initially be caused by abnormal motility and cause pain which on its turn may induce abnormal motility phenomena. The initial impact of the chemical composition of the refluxed material may be of less importance. The consequence of this vicious circle of GER inducing GER leads very rapidly to reflux esophagitis in which the noxious effect of acid on the esophageal mucosa may become more important than pain. In this case, initial treatment should by preference focus on motility and for the treatment of (severe) esophagitis, medications reducing acid such as proton pump inhibitors may recommended.[5]

In the ferret, at least three types of esophageal afferent fibers exist, namely mucosal, tension and tension/mucosal fibers.[26] Vagal efferent neurons respond to gastroesophageal mechanical inputs, and also receive convergent input from esophageal acid-sensitive and gastrointestinal bradykinin- and capsaicin-sensitive afferents. Sudden rapid stretch of the mechanoreceptors in the proximal esophagus can trigger the hiccup reflex in normal subjects.[27] Only rapid distensions above a determined volume threshold will predictable induce hiccups in a given subject.

ESOPHAGEAL CLEARANCE

Esophageal clearance is influenced by at least three factors: esophageal peristaltic waves, gravitation and saliva. Delayed clearance of acid from the esophageal and decreased pressure of the LES are the major mechanisms involved in the development of esophagitis.[28] Swallowed saliva contributes to the neutralization of the refluxed acid. The bolus-effect of swallowed saliva will help in clearing the esophagus from the refluxed material. The amplification of peristaltic clearing may be considered the initial protective process aganints acid reflux.[29]

Interstitial cell of cajal (ICC) is most frequent in the esophageal part of the LES but rare in the gastric part of esophagus.[30] The role of ICC in inhibitory transmission in the LES is still discussed. Loss of ICC during development or in pathologic condition such as GERD significantly compromise the ability of GI muscles to generate motor reflexes. Esophagitis itself may be the origin of alteration of normal funtion ICC.[31] In advanced stages of GERD, the inflammation in the wall of esophagus will diretly involve ICC. The more severe the esophagitis the more severe is ICC impairment. ICC impairment means impairment in esophageal peristalsis, impairment in esophageal clearance, maintaining reflux material and aggravating the symptoms.[32]

ESOPHAGEAL MUCOSAL RESISTANCE

The resistance of the mucosa the noxious effect of the refluxed material (acid, pepsin, chymotrypsin and trypsin, bile, etc.) is different from person to person. Prostaglandin E2 and nitric oxide (NO) are protective and detrimental factors for esophageal mucosal integrity.[33] HCl or pepsin is related to a further increase of prostaglandin E2 secretion in comparison to saline. Release of prostaglandin differs for the subtypes and in function of the composition of the refluxed material. Non steroid anti inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins.[34]

LOWER ESOPHAGEAL SPHINCTER AND TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS

The lower esophageal sphincter (LES) is a functional barrier, and represents a zone with an intraluminal pressure that is greater than that of the stomach and esophagus. The LES pressure is a defense mechanisms to prevent GER. The LES pressure decreases postprandially. Gastric contractions, gastric

alkalanization and proteins increase the LES pressure. Gastrin, motilin and substance P increase the pressure of the LES. Some substrat also reported decrease the pressure of the LES, such as fat, progesteron, atropine, cholecystokinin, glucagon, vasoactive intestinal peptide (VIP), nitric oxide (NO), dopamine, secretin, estrogen, nicotine, alcohol, mint and chocolate. Although atropine decreases the LES-pressure, it also decreases reflux by inhibiting the TLESRs.[35]

Gastric distension is accompanied by a fall in LES-pressure or by inappropriate TLESRs. These responses are mediated via vagal reflexes. TLESRs is LES relaxation which is not related to the process of swallowing and lasting longer than usual, regulated by afferent side mechanoreceptor on the wall of the proximal stomach, whereas efferent side is regulated by the brain stem.[36-38]

TLESR occur concurrent with curved diaphragm and esophageal body inhibition, making the backflow of gastric contents into the esophagus easier. This situation is often occurs after eating and is triggered by gastric distension, so the disturbance of gastric emptying will increase the frequency TLESRs. When there are TLESRs, LES pressure reduced to zero so it does not serve as an anti-reflux barrier. It was reported that 70-90% in children with reflux episode with GER are associated with TLESRs.[36] Other report shows that there are 100% TLESRs on physiologic reflux and 66% TLESRs in severe esophagitis case. Although further assessment is still necessary, based on observations it can be concluded that TLESR may play a role in pathologic GER and the development of GERD. Many other conditions such as use of intubation, anesthesia, sleep, and stress also reported to increase the frequency TLESR.[36] Most reflux episodes occur in relation to TLESRs. TLESRs are the predominant mechanism of GER in healthy preterm infants. TLESRs are more frequent in the seated position than in supine position, reflux occurs most in the seated position, followed by the supine position and the lowest is in prone position.[37,38]

Gastric distension and partial or incomplete swallowing induce TLESRs, which are also the normal mechanism for burping and belching. Regurgitation can be considered as a natural defense mechanism for overfeeding: when the stomach becomes too distended, TLESRs are induced more frequently, allowing the feeding to flow back in the esophagus. During sleep, there are normally no TSLESs. TLESRs are the major mechanism causing GER(-disease). However, the cause is not clear yet.[36,37]

INTRA-ABDOMINAL ESOPHAGUS AND ANGLE OF INDENTATION

The length of the intraabdominal esophagus is shortened or non-existent in patients with a hiatal hernia. As a consequence, the LES region is located in the thorax, has a negative pressure and cannot function as a high pressure zone. As a consequence the gastric content is "aspirated" back into the esophagus because of the pressure differences between abdomen and thoracic cavity. During the first years of life, the length of the intra-abdominal esophagus is physiologically very short, which contributes to the increased incidence of regurgitation in this age group.[39]

The angle between the great curvature of the stomach and the esophagus is obtuse and favors GER-episodes in hiatal hernia. The angle is more obtuse in young infants, and only becomes acute after the age of one year. Esophageal acid exposure is greater in the right side sleeping position than in left position. Esopagheal clearance is delayed in right side position.[40]

GASTRIC VOLUME, EMPTYING, AND ACID OUTPUT

Mechanoreceptors are present in the fundus, near to the gastric part of the cardiac region. When these are stimulated because of gastric distension will induce TLESRs. The role of the vagal nerve endings in the esophagus could possibly be involved in this mechanism.The frequency of postprandinal GER is related to the meal size. Gastric bolus feeding is related to greater intragastric pressure causes more TLESRs. Osmolality and volume of the feeding slow gastric emptying and incrase postprandial GER.[41] There is a very large variation in the secretion of gastric acidity during a 24-hour period. The vagal nerve regulates gastric acid secretion. The noxious effect of pepsin on the esophageal mucosa is greater than that of acid. The effect of bile salts influenced by the pH of the refluxed material. Bile salts increase the permeability of the esophageal mucosa to acid.[42]

GASTROESOPHAGEAL REFLUX DISEASE

Definition of gastroesophageal reflux disease (GERD) is met when reflux symptoms and complications (such as heart burn, hoarseness, chronic cough or nightly cough, failure to thrive, Sandiffer syndrome) or when there is morphological changes in the esophageal mucosa (thickening layer of basal cells, inflammatory in filtration by neutrophils or eosinophils,

erosion, ulceration, metaplasia of the mucosa) is caused by GERD.[43,44] GERD symptoms can be grouped into two major group, esophageal and extra-esophageal symptoms.[45-47]

The occurrence of GERD is associated with whether or not the preventive factors are functioning. When these preventive factors are functioned properly then the cases of GERD can be avoided. Preventive factor early on is the process of mastication and lubrication of food material by saliva, this process grinds the food so it does not injure the esophagus and is also easier for the stomach to digest food so gastric emptying increases. Impaired gastric emptying, will have 2 times higher risk of experiencing a pathological reflux.[11,48]

Other preventive factors for GERD are esophageal peristalsis, secretion and mucosal resistance, gravity and position, the LES tone, and angle of his. Prevention mechanisms are mutually work together to prevent the occurrence of GERD and its complications. Peristalsis cleaning reflux material, secretions reduce the acidity of the reflux material and reduce the inflammation that occurs because as a result of the contact of the acid on the esophageal mucosa, there is an increase in the regional blood flow, increasing prostaglandin E2 of the local tissue. Prostaglandin increases the permeability of the mucosa to acid, which enhances the suspectibility of the mucosa for inflammation.[49] Inflammation causes an impairment and dysmotility of the LES (favoring GER), finally causing esophagitis. The contact of acid on the esophageal mucosa causes inflammation of the local vagal nerve endings, causing an impairment of the LES and a pylorospasm.[49] Prevalence reflux esophagitis is 15-62% in children age 0-17 years with GER symptoms.[50] A study in Indonesia by Lia et al in Cipto Mangunkusumo Hospital in 2007-2008 showed that 18 of 21 children (85.7%) with GERD had reflux esophagitis[51] and these results are also consistent with studies conducted in India with 26 of 33 children (78.8%).[52]

Barrett's esophagus (BE) occurs in children with much less frequency than it does in adults. Multiple biopsies documented in relation to endoscopically identified esophagogastric landmarks are advised to confirm or rule out the diagnosis of BE and dysplasia.[5,50] In BE, aggressive acid suppression is advised by most experts. Symptoms are a poor guide to the severity of acid reflux and esophagitis in BE, and pH studies are often indicated to guide treatment. BE per se is not an indication for surgery.[5,50]

Gravity may help clearance of reflux material, position also affect the reflux, GER occurs more frequently in seated position followed by supine and prone at the lowest.[53] LES tone and angle of his are important preventive mechanism for reflux because the pathogenesis of the most important in the case of GERD is the increasing TLESRs.[37,38] Most of these preventive factors involved the esophagus itself, so when there is patient with GERD we shouldn't forget to search any disturbances on these factors.

CONCLUSION

The most typical, although unspesific of a symptoms of esophageal dysfunction are gastro-esophageal reflux, regurgitation and vomiting. GER can in fact also be considered as part of esophageal function as a protective mechanism. GER disease is a spectrum of disease that can be defined as the symptoms and/or signs of esophageal or adjacent organ injury seconday to the reflux of gastric contents into the esophagus.

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