International Journal of New Technology and Research (IJNTR)
ISSN:2454-4116, Volume-2, Issue-3, March 2016 Pages 04-08

Esophageal Motility Disorder in Gastrophageal Reflux Disease

Grande M, Lisi G, Grande S, Campanelli M, Villa M

***Abstract*— Gastroesophageal reflux disease (GERD) represents a real social problem in the western world. Brazilian consensus conference considered GERD to be "a chronic disorder related to the retrograde flow of gastro-duodenal contents into the esophagus and/or adjacent organs, resulting in a spectrum of symptoms, with or without tissue damage". However, gastro-esophageal refluxate contains a variety of other noxious agents, including pepsin. Currently, it is recognized that this component of the refluxate (commonly called bile reflux and identified by the Bilitec bile reflux monitor using bilirubin as a marker) is composed of bile salts and pancreatic enzymes, and is also injurious to the esophageal mucosa. It causes symptoms, and could be linked to the development of Barrett's esophagus and esophageal adenocarcinoma. A highly efficient barrier exists between the stomach and the esophagus formed by the lower esophageal sphincter, the diaphragm, the His angle, the Gubaroff valve and the phrenoesophageal membrane. The most important factors at work in preventing reflux include, well the lower esophageal sphincter, esophageal clearance mechanisms that limit contact time with noxious substances, and mucosal protective factors intrinsic to the esophageal mucosa. The most common cause of gastroesophageal reflux is an excessive exposure of the esophagus to gastric secretions during Transient Lower Esophageal Sphincter Relaxation. pH-metric studies in healthy subjects have shown that primary peristalsis is the most important mechanism of clearing after acid reflux in orthostatic position. When the subject is in supine position, however, most reflux is neutralized by means clearance produced by secondary peristalsis. Several studies have shown that oesophageal function is impaired in patients with reflux oesophagitis, especially in high grade oesophagitis. Patients with reflux oesophagitis have reduced lower oesophageal sphincter pressures, an increased incidence of failed peristalsis, reduced distal peristaltic amplitudes, slower velocity of propagation and in some studies shorter duration of contractions. In conclusion, application of the 24hour ambulatory oesophageal pressure and pH monitoring technique did not show any differences in either pH profiles or motility variables before and after healing of reflux oesophagitis. The fact that oesophageal motility does not change after healing of oesophagitis supports the hypothesis that abnormalities in motility are pre-existent rather than the consequence of the inflammation. It could be argued, however, that the inflammation has caused irreversible changes in the oesophageal wall.**

Simona Grande, Department of Surgery, University of Messina, Italy
Michela Campanelli, Department of Surgery, University of Modena, Italy
Giorgio Lisi, Department of Surgery, Univeristy of Verona, Borgo Roma, Italy
Massimo Villa, Department of Surgery, University Hospital of Tor Vergata, Rome, Italy

I. INTRODUCTION

Gastroesophageal reflux disease (GERD) represents a real social problem in the western world about 20% of population has at least once a week, typical symptoms of this disease (heartburn and acid regurgitation); this incidence is probably underestimated because many patients have symptoms referable to extra-esofageal locations (asthma, cough, hoarseness, non cardiogenic chest pain). The Montreal consensus conference defined GERD as "a condition that develops when the reflux of gastric contents causes troublesome symptoms and/or complications" [1]. But this definition does not take into account all possible pathogenetic causes and their therapeutic implications. Therefore seems more relevant to the definition of Brazilian consensus conference who considered GERD to be "a chronic disorder related to the retrograde flow of gastro-duodenal contents into the esophagus and/or adjacent organs, resulting in a spectrum of symptoms, with or without tissue damage" [2]. This definition recognizes the chronic character of the disease, and acknowledges that the refluxate can be gastric and duodenal in origin, with important implications for the treatment of this disease [3].

Gastric hydrochloric acid has long been recognized as harmful to the esophagus [4]. However, gastro-esophageal refluxate contains a variety of other noxious agents, including pepsin. Currently, it is recognized that this component of the refluxate (commonly called bile reflux and identified by the Bilitec bile reflux monitor using bilirubin as a marker) is composed of bile salts and pancreatic enzymes, and is also injurious to the esophageal mucosa [5]. It causes symptoms, and could be linked to the development of Barrett's esophagus and esophageal adenocarcinoma [6].

Besides the constituents of the refluxate, symptom perception and mucosal damage also appear to be linked to the patterns of esophageal exposure and the volume of the refluxate. Individuals are more likely to perceive a reflux event if the refluxate has a high proximal extent and a large volume [5].

A highly efficient barrier exists between the stomach and the esophagus formed by the lower esophageal sphincter (LES), the diaphragm, the His angle, the Gubaroff valve and the phrenoesophageal membrane [6].

The most important factors at work in preventing reflux include, well the lower esophageal sphincter, esophageal clearance mechanisms that limit contact time with noxious substances, and mucosal protective factors intrinsic to the esophageal mucosa.

The LES, a 3 to 4 cm long region of smooth muscle located at the esophagogastric junction, creates a zone of high

pressure separating the esophageal and gastric compartments between swallows. The diaphragmatic crura assist the LES in the maintenance of a tonically closed sphincter. The hiatus hernia eliminates the contribution of the crural diaphragm to LES function and thereby promotes gastroesophageal reflux. The severity of reflux disease in patients with hiatal hernia has been positively correlated with the size of the hernia sac [7].

The most common cause of gastroesophageal reflux is an excessive exposure of the esophagus to gastric secretions during Transient Lower Esophageal Sphincter Relaxation (TLESR). The initial event is in a sharp decrease in the tone pressure not triggered by swallowing or esophageal contractions. The duration of TLESR (about 10 seconds) is greater than those induced by swallowing (about 6-8 seconds) and is accompanied by gastroesophageal reflux.

Has been shown that TLESR occur with a frequency of 2-6 episodes for hour in normal subjects and increased in patients with GERD (3-8 episodes). In normal subjects, in fact, only 40-50% of such releases is followed by acid reflux while the percentage rises to 60-70% in patients with GERD [8].

In healthy subjects showed reduced LES pressure in the postprandial period and during exercise; most reflux episodes (82%) occur during TLESR. The mechanism behind this release inappropriate is not yet clarified; some results suggest that this release occur in response to gastric distention and vagal stimulation.

The gastric distension is probably able to trigger such releases through the stimulation of mechanoreceptors located in the proximal stomach in the vicinity of the LES [8].

Each time that gastric contents refluxing into the esophagus the extent of esophageal mucosal injury depends on several factors including the contact time between refluxate and the mucosa, the composition of refluxate and the intrinsic ability to resist damage the esophageal epithelium [9]. As the capacity of the refluxate to cause inflammation and then symptoms depends on the time of contact between the esophageal mucosa and the acid content of the refluxate a prompt and speedy clearance of the refluxate is of primary importance. Acid clearance normally occurs as a two steps process. At first most of the refluxed volume is cleared quickly by one or two peristaltic contractions, thereafter the remaining acid is neutralised by swallowed saliva [10]. Secondary peristalsis is triggered by esophageal distension and contributes to esophageal volume clearance after reflux [11]. It is the initial esophageal motor event after most reflux episodes in normal subjects.

In fact, pH-metric studies in healthy subjects have shown that primary peristalsis is the most important mechanism of clearing after acid reflux in orthostatic position. When the subject is in supine position, however, most reflux is neutralized by means clearance produced by secondary peristalsis. The contact time between the esophageal mucosa and a acid reflux potentially damaging increase during sleep when esophageal clearance is greatly reduced due to the decrease in the number of swallowing, the volume and alkalinity of the saliva and the absence of gravity [12].

The esophageal acid clearance is a process that takes place in two stages. On the one hand, the volume of the refluxate is removed by esophageal peristalsis, the other the acid pH is neutralized by bicarbonate rich saliva delivered by primary peristaltis.

Thus secondary peristalsis would not by itself be expected to restore esophageal pH, but to complement and accelerate the effects of the primary peristalsis that follows [11].

In normal subjects during concurrent ambulatory manometry and pH monitoring that while primary peristalsis was the most common initial esophageal clearance event overall, secondary peristalsis was the important initial motor event when the subjects were supine or asleep, or both [13].

Several studies have shown that oesophageal function is impaired in patients with reflux esophagitis, especially in high grade esophagitis. Patients with reflux oesophagitis have reduced lower esophageal sphincter pressures, an increased incidence of failed peristalsis (Fig. 1), reduced distal peristaltic amplitudes, slower velocity of propagation and in some studies shorter duration of contractions [10]. Two groups have reported that healing of oesophagitis does not improve impaired oesophageal motility [14,15].

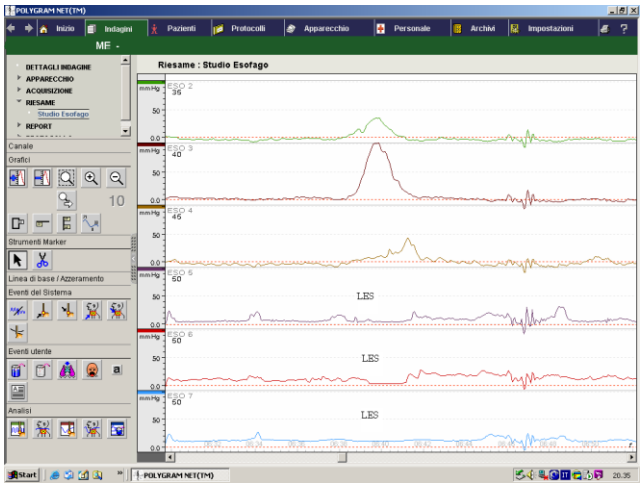

Fig. 1. Esophageal Manometry in Patients with Gastroesophageal Reflux with Perfusion Catheter to 6-way, three of which radial. Presence of low pressure LES and waves of low amplitude in the Distal Esofagus. (*Grande et al.)*

An extension of the clearance time has been reported in about 50% of patients with esophagitis [16]. The frequency of abnormalities of peristalsis increases with the severity of reflux reaching 20% in patients with GERD without esophageal lesions (Fig. 2), 25% in those with moderate esophagitis, and 48% in those with severe esophagitis [16]. A weak or ineffective peristalsis (waves of amplitude less than 30/40 mm Hg) is not able to eliminate acid reflux from the esophagus [16].

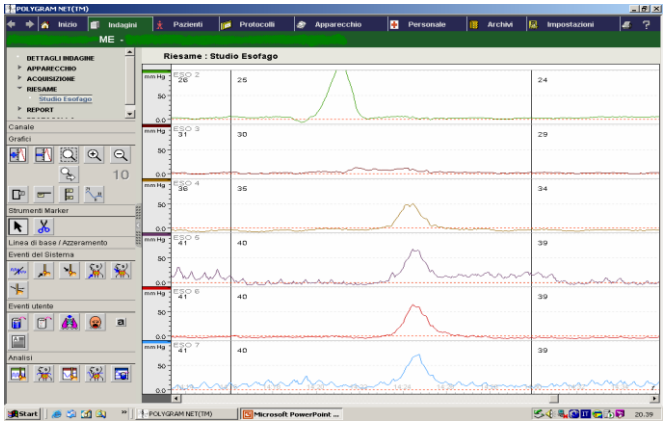

Fig. 2. Esophageal Manometry with perfusion catheter to 6-way, three of which radial. Failed Peristaltis in patients with Gastroesophageal reflux. (*Grande et al.*)

Even a lack of salivary function, characterized by reduced secretion or a reduced capacity for neutralization by saliva may result in a prolongation of esophageal clearance [12]. For example, smokers have a reduced salivary secretion than nonsmokers and therefore have a higher incidence of GERD.

The velocity of propagation has been shown to be slower in patients with reflux esophagitis. Savarino et al have reported shorter durations of contraction in this condition [15]. On the other hand, Ghoshal et al have found a longer duration of contraction in patients with GERD compared with the controls [17]. esophageal transit and acid clearance have also been shown to be slower in these patients [15]. In agreement with those observations Moore et al found, comparing oesophageal motility in patients with low grade esophagitis with motility data obtained in a matched normal control group, reduced propagation velocity and duration of peristaltic contractions, with increase in the number of non transmitted contractions in patients with grade I and II oesophagitis. Peristaltic amplitude was not shown to be impaired [10].

Defective peristalsis is associated with severe GERD, both in terms of symptoms and of mucosal damage [18]. As matter of fact, the composite reflux score (DeMeester score) includes in its calculation two indirect measurements of esophageal clearance (number of reflux episodes longer than 5 min and length of the longest episode) (Fig. 3-4). In addition, the average esophageal clearance time can be calculated by dividing the total minutes the pH is below 4 by the number of reflux episodes [19]. This association also explains the high prevalence and severity of GERD in systemic diseases that affects peristalsis, such as connective tissue disorders [20].

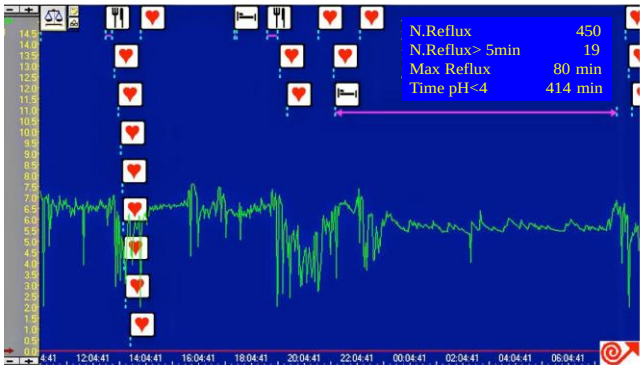

Fig. 3. 24-hour pH-metry with antimony probe. Patients with Pathological acid reflux (pH <4 lasting more than 5 minutes) in the upright period. (*Grande et al.*)

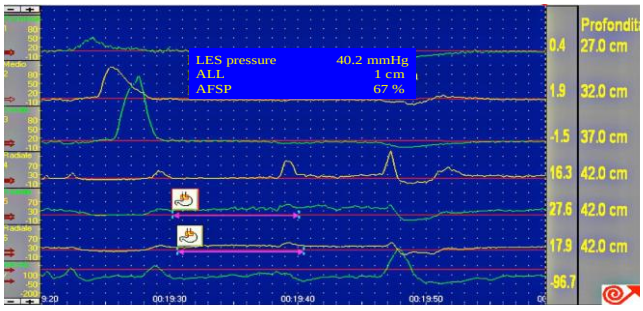

Fig. 4. Same as preceding case. Manometric examination shows reduced abdominal LES length with abnormal frequency of successful primary peristalsis, median response rate in this subject of only 33%. (*Grande et al.*)

It is known that 40%-50% of patients with GERD have abnormal peristalsis [18]. This dysmotility is particularly severe in about 20% of patients because of very low amplitude of peristalsis and/or abnormal propagation of the peristaltic waves (ineffective esophageal motility) [21]. Esophageal clearance is slower than normal, therefore, the refluxate is in contact with the esophageal mucosa for a longer period of time and it is able to reach more often the upper esophagus and pharynx. Thus, these patients are prone to severe mucosal injury (including Barrett's esophagus) (Fig.5) and frequent extra-esophageal symptoms such as cough [3, 21, 22].

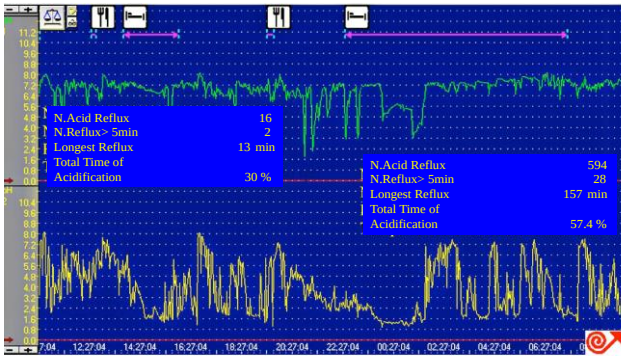

Fig. 5. 24-hour pH-metry with antimony probe with two-way read points located 10 cm apart. Presence of reflux in both upright and in supine position coming up. (*Grande et al.*)

In addition to alterations of primary peristalsis patients with GERD have disorders secondary peristalsis and most of

them the esophageal distension is not capable of triggering secondary peristaltic contractions [23]. As this deficit can occur even in subjects with normal primary peristalsis has been suggested that the phenomenon is due to an altered response to esophageal acid reflux and / or relaxing [11]

Patients with reflux disease have considerably lower secondary peristaltic response rates than have aged matched controls with most patients failing to trigger any peristaltic response at all [11]. This finding supports and extends earlier findings on spontaneous reflux episodes, which showed that secondary peristalsis occurred less frequently after reflux in patients with reflux oesophagitis compared with normal subjects [24].

Secondary peristalsis is a reflex response to oesophageal distension, the defect may lie in the esophageal motor nerves or muscles oesophageal sensation, the central integrative mechanisms or a combination of these. Most patients with abnormal primary peristalsis also had abnormal secondary peristalsis and in these patients we postulate that the defect lies in the efferent limb of the motor pathway [11]. Most patients with abnormal secondary peristalsis, however, had normal primary peristalsis. Because secondary peristalsis seems to share a common motor pathway with primary peristalsis this side of the reflex would seem to be intact, implying that the defect in secondary peristalsis is due either to an abnormality of oesophageal sensation or in the integration of sensory information with the motor component of the reflex [11]. This hypothesis is supported by the findings of Williams et al who noted that the distension threshold required to trigger a motor response was higher in patients with oesophagitis than in healthy controls [23]. Others, however, have found no difference in the threshold volume required to trigger oesophageal motor responses using slow (1 ml/s) infusions [25]. Differences in the methods of these studies, however, make direct comparisons of these results difficult. Secondary peristalsis can effectively clear almost all of an injected acid bolus from the esophagus leaving a negligible residual volume [11]. However, changes in esophageal pH would be unlikely until neutralization of the residual acid by bicarbonate rich saliva delivered by primary peristalsis [11]. Thus secondary peristalsis would not by itself be expected to restore oesophageal pH, but to complement and accelerate the effects of the primary peristalsis that follows. During the day when patients are awake, any effect of defective secondary peristalsis on acid clearance will be minimised by frequent primary peristalsis. Secondary peristalsis is likely to be more important, however, during sleep when the rate of primary peristalsis is substantially reduced [26].

While there is no dispute that these abnormalities are commonly present in patients with reflux oesophagitis, there is a continuing debate as to whether these are primary phenomena or the consequences of repetitive injury and inflammation caused by acid reflux. Currently, the most reliable data is that the abnormalities of oesophageal motor function in patients with reflux esophagitis do not improve after complete healing of esophagitis [15]. This suggests that esophageal dysmotility in this condition is a primary phenomenon and not a consequence of injury and inflammation. In that regard were detected a high prevalence of impairment of vagal cardiovascular reflexes in patients with gastro-esophageal reflux disease [27].

A dysfunction of the parasympathetic system in the form of vagal neuropathy may help explain some of the changes found in the gastro-esophageal reflux disease (abnormalities of peristalsis, delayed esophageal transit, reduced LES pressure and delayed gastric emptying).

Other studies have shown that patients with reflux disease have a lower sensitivity threshold to esophageal distension compared with control subjects [28]. These patients have a normal acid exposure time but often complain of reflux symptoms. This suggests that some of them have a significantly increased esophageal sensitivity with a consequent increase in the perception of normal reflux (Fig. 6).

It is still unclear whether esophageal dysmotility is a primary condition that leads to GERD, or it is a consequence of esophageal inflammation. Medical therapy does not ameliorate esophageal peristalsis [29,30].

However it has been shown that effective fundoplication improves the abnormal peristalsis in most patients [6]. The operation controls reflux because it improves esophageal motility, both in terms of LES competence and quality of esophageal peristalsis.

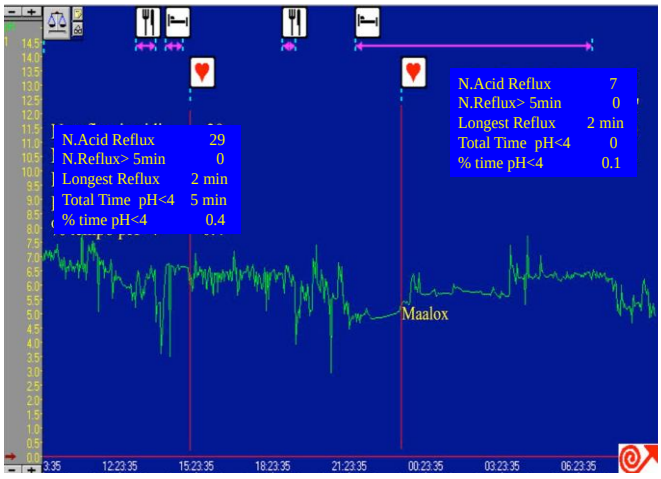

Fig. 6. 24-hour pH-metry probe with antimony. Patient that in the absence of acid reflux disease makes use of antacids. Esophageal hypersensitivity? (*Grande et al.*)

In conclusion, application of the 24hour ambulatory oesophageal pressure and pH monitoring technique did not show any differences in either pH profiles or motility variables before and after healing of reflux esophagitis. The fact that esophageal motility does not change after healing of oesophagitis supports the hypothesis that abnormalities in motility are pre-existent rather than the consequence of the inflammation. It could be argued, however, that the inflammation has caused irreversible changes in the esophageal wall.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

MG: Manuscript Preparation, Interpretation of data and Critical Review.
SG: Acquisition data and drafting the manuscript.
MC: Acquisition and processing data.
GL: Literature review and manuscript preparation.
All authors read and approved the final manuscript

REFERENCES

[1] Vakil, N.; van Zanten, S.V.; Kahrilas, P.; Dent, J. & Jones, R. (2006). The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *American Journal of Gastroenterology*, Vol.101, N.8, pp. 1900-1920, ISSN 0002-9270
[2] Moraes-Filho, J.; Cecconello, I.; Gama-Rodrigues, J.; Castro, L.; Henry, M.A.; Meneghelli, U.G. & Quigley, E. (2002). Brazilian consensus on gastroesophageal reflux disease: proposals for assessment, classification, and management. *American Journal of Gastroenterology*, Vol.97, N.2, 241-248, ISSN 0002-9270
[3] Herbella, F.A. & Patti, M. G. (2010). Gastroesophageal reflux disease: From pathophysiology to treatment. *World Journal of Gastroenterology*, Vol.16, N.30, 3745-3749, ISSN 1007-9327
[4] Herbella, F.A.; Nipominick, I. & Patti, M.G. (2009). From sponges to capsules. The history of esophageal pH monitoring. *Disease of the Esophagus*; Vol.22, N.2, 99-103, ISSN 1120-8694
[5] Tack, J.; Koek, G.; Demedts, I.; Sifrim, D. & Janssens, J. (2004). Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both? *American Journal of Gastroenterology*, Vol. 99, N.6,pp. 981-988, ISSN 0002-9270
[6] Herbella, F.A.; Tedesco, P.; Nipomnick, I.; Fisichella, P.M. & Patti, M.G. (2007). Effect of partial and total laparoscopic fundoplication on esophageal body motility. *Surgical Endoscopy*, Vol.21, N.2, 285-288, ISSN 0930-2794
[7] Lowe, R. C. (2006). Medical management of gastroesophageal reflux disease. *GI Motility online* doi:10.1038/gimo54
[8] Kim SE, Soffer E. Electrical stimulation for gastroesophageal reflux disease: current state of the art. *Clin Exp Gastroenterol*, 2016 Jan 14;9:11-9.
[9] Sun X, Ke M, Wang Z. Clinical features and pathophysiology of belching disorders. *Int J Clin Exp Med.* 2015 nov 15;8(11):21906-14
[10] Moore M, Afaneh C, Benhuri D, Antonacci C, Abelson J, Zarnegar R. Gastroesophageal reflux disease: A review of surgical decision making. *World J gastrointest Surg.* 2016 Jan 27;8(1):77-83.
[11] Simrèn M, Silny J, Hollway R, Tack J, Janssens J, sifrim D. Relevance of ineffective oesophageal motility during oesophageal acid clereance. *Gut.* 2003 Jun;(6):784-90
[12] Review article: gastro-oesophageal reflux disease-pathophysiology issues of clinical relevance. *Aliment Pharmacol Ther*. 2002 Jul;16 Suppl 4:65-71
[13] Characteristics of oesophageal bolus transport in patients with mild oesophagitis. *Eur J Gastroenterol Hepatol.* 2005 Mar;17(3):323-32
[14] Hu Y, Li M, Lu B, Meng L, Fan Y, Bao H. Esophageal motility after peroral endoscopic myotomy for achalasia. *J Gastroenterol.* 2015 Oct 25
[15] Savarino E, Giacchino M, Savarino V. Dysmotility and reflux disease. *Curr Opin Otolaryngol Head Neck Surg*. 2013 Dec;21(6):548-56
[16] Mello M, Gyawaii CP. Esophageal manometry in gastroesophageal reflux disease. *Gastroenterol Clin North Am*. 2014 Mar;43(1):69-87
[17] Ghoshal UC, Daschakraborty SB, Singh R. Pathogenesis of achalasia cardia. *World J Gastroenterol*. 2912 Jun 28;18(24):3030-7
[18] Diener, U.; Patti M.G.; Molena, D.; Fisichella, P.M. & Way, L.W. (2001). Esophageal dysmotility and gastroesophageal reflux disease. *Journal of Gastrointestinal Surgery*, Vol. 5, N.3: 260-265, ISSN 1091-255X
[19] Gerson LB, Triadafilopoulos G. A prospective study of oesophageal 24-h ambulatory pH monitoring in patients with functional dyspepsia. *Dig Liver Dis*. 2005 Feb;37(2):87-91
[20] Patti, M.G.; Gasper, W.J.; Fisichella, P.M.; Nipomnick, I. & Palazzo, F. (2008). Gastroesophageal reflux disease and connective tissue disorders: pathophysiology and implications for treatment. *Journal of Gastrointestinal Surgery*, 12(11): 1900-1906, ISSN 1091-255X
[21] Patti, M.G. & Perretta, S. (2003). Gastro-oesophageal reflux disease: a decade of changes. *Asian Journal of Surgery*, Vol.26, N.1, pp. 4-6, ISSN 1015-9584
[22] Meneghetti, A.T.; Tedesco, P.; Damani, T. & Patti, M.G. (2005). Esophageal mucosal damage may promote dysmotility and worsen esophageal acid exposure. *Journal of Gastrointestinal Surgery*, Vol.9, N.9, 1313-1317, ISSN 1091-255X
[23] Oshima T, Miwa H. Pathogenesis of gastro-esophageal reflux disease. *Nihin Rinsho*. 2007 May;65(5):797-801
[24] Ulualp SO, Brodsky L. Monitoring of gastric acid suppression in patients with extraesophageal reflux disease. *In J Pediatr Otorhinolaryngol*. 2007 Dec;71(12)1849-53
[25] Savarino E, Tutuian R. Combined multichannel intraluminal impedance and manometry testing. *Dig Liver Dis.* 2008 Mar;40(3):167-73
[26] Orr WC. Reflux events and sleep: are we vulnerable?. *Curr Gastroenterol Rep*. 2006 Jun;8(3):202-7
[27] Pirtniecks A, Smith LF, Thorpe JA. Autonomic dysfunction in non-specific disorders of oesophageal motility. *Eur J Cardiothorac Surg.* 2000 Feb;17(2):101-5
[28] Remes-Troche JM, Chahal P, Mudipalli R, Rao SS. Adenosine modulates oesophageal sensorimotor function in humans. *Gut.* 2009 Aug;58(8):1049-55.
[29] Sasso G, Rambaldi P, Sasso FS, Cuccurullo V, Murino P, Puntieri P, Marsiglia HR, Mansi L. Scintigraphic evaluation of oesophageal transit during radiotherapy to the mediastinum. *BMC Gastroenterol*. 2008 Nov 5;8:51
[30] Xu, J.Y.; Xie, X.P.; Song , G.Q. & Hou, X.H. (2007). Healing of severe reflux esophagitis with PPI does not improve esophageal dysmotility. *Diseases of the Esophagus*, Vol.20, N.4, pp. 346-352, ISSN 1120-8694