Clinical Manifestation and Management of Extra-Esophageal Gastroesophageal Reflux Disease

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ABSTRACT

GERD is a condition that gastric content go back into the esophagus. This condition could came disturbances in the respiratory tract, heart and otolaryng. Those extra-esophageal clinical manifestation are common but often miss our attention. So it is important to explorate it further. The management of extra-esophageal GERD is similar with management of GERD. It is included life style modification and reducing refluxate with controlling pH with aggressiveness.

***Key Words**: Extra GERD, non cardiac chest pain, respiratory disturbance, omeprazole.*

INTRODUCTION

Wright, et al, evaluated 30 non-smoking asthmatic patients with symptoms of gastroesophageal reflus disease (GERD) confirmed by pH-Metry, the effect of 20-60 mg of omeprazole, 20 (67%) of which with improved asthmatic symptoms, and 6 (20%) with increased Peak Flow Rate (PFR).[1]

From the questionnaires distributed to 109 Canadians with asthma divided into 2 groups: the study subject and control group. In the study subjects with the following symptoms reported: 77% with heartburn, 55% with regurgitation, and 24% with dysphagia, the incidence of asthmatic attacks were more significant than in control subjects.[2] Since 1986, there have been many reported studies on the relationship between esophagus and non-cardiac chest pain. The relationship varies according to the study subject and diagnostic criteria. In 27 out of 30 patients (90%), chest pain did not indicate signs of ischemia.[3]

Extra-esophageal clinical manifestation of GERD are common, but often miss our attention. Thus it is important to analyze it further. This paper will discuss the anatomy, pathophysiology, clinical manifestation and management.

ANATOMY AND HISTOLOGY

A physician who intends to diagnose and manage esphageal disorder should have knowledge of normal esophageal anatomy, pathologic changes during initial stages and optimal evaluation of each method for the evaluation of esophageal function and morphology.[4]

The adult esophagus is a flat muscular cylinder from the pharyngoesophageal junction (5^{th}-6^{th} cervical vertebrae) through the back of the mediastinum, ending on the gastroesophageal junction (first thoracal vertebrae). The esophageal cavity could distend as much as 2 cm to the front and back, and 3 cm to its sides. The length of the adult esophagus varies from 18 to 26 cm. The esophagus at the cervical region, from the pharyngoesophageal junction to the suprasternal point is approximately 4-5 cm. At this level, the esophagus is bordered by the front of the trachea, the vertebrae and the carotis and thyroid membranes at each side.[5]

The thoracal portion of the esophagus passes through the back to the tracheal wall and the back branch of the right aorta (Thoracal 4), and then to the branches of the trachea and the main bronchus, crossing the front of the aorta at the diaphragmatic hiatus. At the level of the 10^{th} thoracal vertebrae, where the esophagus passes an open

space shaped like an ellipse on the diaphragmatic muscle and into the cardia of the gaster at an oblique angle.

At the level of the diaphragm, the esophagus is surrounded by elastic collagen fibers from the phrenoesophageal membrane.

BLOOD FLOW[6]

The arterial blood flow to the esophagus is an extensive and overlapping segmental flow. The cervical portion receives its blood flow mainly from the inferior branch of the thyroid artery. Additional arterial branches are the carotid, vertebral, subclavic and ascending pharyngeal arteries.

The thoracal portion of the esophagus receives its blood flow from the right intercostal and the bronchial branches of the aorta. The abdominal portion of the esophagus receives its blood flow from branches of the left gangster and the lower left pricnicus artery.

We have adequate knowledge of the anatomy of the esophageal vein. The intraepithelial flow is collected into the sub-epithelial superficial venous plexus. This plexus flows into the intrinsic vein in the sub-mucosa.

INNERVATION

The vagal nerve only innervates the esophagus parasymphatetically, even though it brings a collection of sympathetic and parasympathetic fibers to the neck. The cervical portion of the esophagus is innervated from the recurrent laryngeal nerve innervate the upper thoracic esophagus. The left and right vagal nerves merge with sympathetic fibers to form the esophageal plexus.[7]

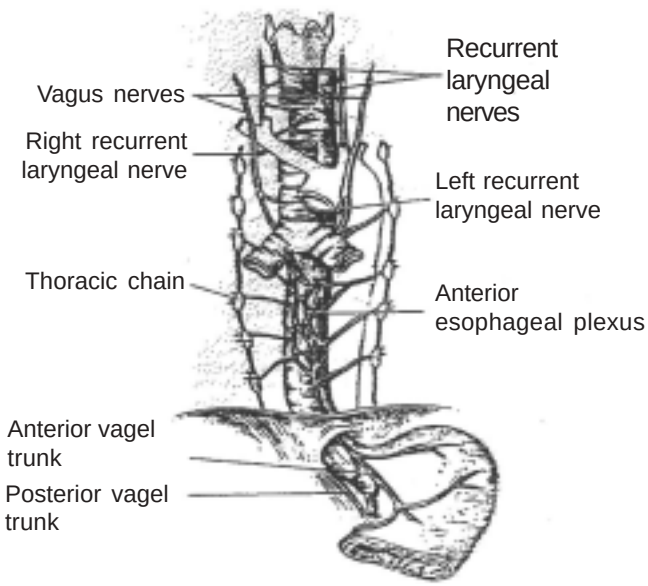

Figure 1. Esophageal innervation

As they leave the esophageal plexus, the anterior and posterior vagal pathways separate. Below the diaphragm, the anterior vagal pathway branches into the hepatic and the anterior gastric branches. The posterior vagal pathway branches to the celiac plexus and the posterior gaster.

The esophageal wall consist of 4 layers: (1) the mucosa membrane, the tunica mucosa, (2) sub-mucosa or tunica sub-mucosa, (3) external muscle or tunica muscularis, (4) tunica adventia.

The inner most layer of the mucosal membrane is made up of non-keratinizing squamous epithelium, which supports the lamina propria tissue and the smooth muscle layer. The squamous epithelium is made up of basal cells as the basal stratum, the prichle cells known as the intermediate stratum and the superficial layer or the superficial stratum.

PATHOPHYSIOLOGY

GERD could cause disturbances in the respiratory tract, heart and otolaryng through 2 chief mechanisms, as follows:

1. Gastropharingeal reflux, with or without small aspirations from the gastric reflux matter causing an inflammatory reaction, known as the Crausaz reflux theory.[9]

   The gastroesophageal reflux can usually be prevented by adequately functioning upper and lower esophageal sphincter. Even though gastric juices often passes through the lower esophageal sphincter, the basal pressure of the esophageal sphincter increases if the reflux causes increased pressure from the esophagus, followed by a reflex to close from the esophagoglotic to protect the respiratory tract from contact with reflux material. Swallowing or coughing could clear the reflux on the upper esophageal sphincter.
2. Stimulation of esophagopulmonary or esophagolaryngeal reflex, where reflux from the distal esophagus stimulate vagal reflex, causing bronchoconstriction. This theory is called the reflex theory.[10] Other mechanisms that play a role is the esophagobronchial reflex, an embryonic-derived portion of the common innervation. Other physiologic protection mechanisms prevent the reflux fluid from entering the larynx-pharynx space. This repellant and protective mechanism could mimic extra-esophageal symptoms found in GERD.

The acidity of the lower esophagus could stimulate sensitive acid receptors, which would then interact with the vagal nerve on the upper respiratory tract. Administration of 0.1 N HCl into the esophagus demonstrates reduces respiratory flow.

In the mean time, very little is known about the afferent sensory mechanism in humans, which could cause chest pain, cough and asthma.[11]

This theory is supported by studies that demonstates that small amounts of acid administered into the respiratory tract could cause bronchial spasm.

According to Gostal, acid reflux into the distal esophagus is commonly found in patients with asthma and chronic cough, but exposure on the proximal esophagus is rarely found, which supports the concept that acid exposure on the distal esophagus could cause the bronchial spasm reflex, while acid exposure on the proximal esophagus could cause chest pain.[12]

CLINICAL FINDINGS

Non-cardiac chest pain

Discomfort on the front chest is a fundamental part of the esophageal chest pain syndrome. The pain is illustrated as a burning sensation, located at the back of the chest, spreading to the back, neck, jaws, or arms, sometimes causing wind-like pain. The pain is usually unconnected with swallowing activities, but may be induced by cold or hot fluids. The pain usually wakens the patient from his or her sleep and gets worse if the patient is emotionally disturbed.[11] Patients with esophageal chest pain usually complain of other esophageal symptoms. For example, out of 100 patients, 74% suffered from pyrosis, 67% from regurgitation, 49% dysphagia, and 14% odinophagia, while 11% did not demonstate esophageal symptoms.

Esophageal chest pain usually occur due to stimulation on chemical receptors (acid, pepsin, bile acid), mechanic receptors (distention, spasm), or thermal receptors (cold).

Long-term monitoring studies on the esophagus demonstrate that GERD is a direct cause of non-cardiac chest pain. In the year 1982, De Meester found a number of GERD patients from 24-hour esophageal monitoring. Twenty-three (46%) of 50 patients with angina-like chest pain were found with normal coronary angiograms.[14] DeCaestecker found abnormal reflux in 14 (28%) out of 50 patients with chest pain of unknown origin. [15] Schofield identified acid reflux in 23 (44%) out of 52 patients with chest pain and normal coronary angiogram, but demonstrated reflux symptoms during treadmill test.[16]

Chest pain due to reflux could also occur in patients with coronary arterial disorder, which is difficult to diagnose. Out of 30 patients, 20 [67] were found with chest pain accompanying acid reflux during long-term esophageal pH monitoring. Four patients also suffered from ischemia, 2 of which caused by acid and 1 with reflux.[17] It has been known that the differential diagnosis of chest pain is hard to determine. The unique symptom of angina pectoris may also be found in patients with chest pain due to esophageal disorders. This could be explained by the fact that the heart and esophagus has the same innervation.[18]

The diagnosis of GERD as a cause of non-cardiac chest pain is based on findings of esophagitis on endoscopy or pathological reflux on 24-hour esophageal pH monitoring. However, sometimes patients with esophagitis cannot be detected using endoscopy. Endoscopy has a sensitivity rate of approximately 50%, while 24-hour esophageal pH monitoring has a sensitivity rate of 80-85%. To increase the sensitivity, we could also use an index of esophageal symptoms such as pyrosis and regurgitation.[19] The algorithm as shown in Figure 1 could be used as guidance for the evaluation of chest pain.

Up to now, the "therapeutic trial" test using high doses of Proton Pump Inhibitors twice daily has been used. This is a sensitive, effective and cheap test to differentiate GERD from non-cardiac chest pain.[20] This study used 40 mg of omeprazole in the morning and 20 mg at night for 7 days.

Respiratory tract disturbance

The cough reflex is induced by stimuli on the epithelial sensory nerve (cough receptor) on the tracheobronchial or laryngeal reflex branch complex transmitted to afferent nerves at the cough center in the brain stem, followed by stimulation of efferent nerves in the diaphragm, larynx, abdominal muscles and thorax to produce cough. GERD could also directly cause chronic cough due to stimulan of receptors in the trachea, larynx, and bronchus by aspiration fluid. It could also go through the esophagobronchial reflex, due to exposure of the acid-sensitive sensory nerves by reflux material. The vagal and superior laryngeal nerve receptor pathway could induce cough when stimulated by respiratory tract secretion, foreign bodies, or tumor. [21] Increased sensitivity of cough receptors could reduce the cough threshold. Such mechanism occurs if angiotensin enzyme inhibitors are used.[22]

GERD has been concluded to be able to cause chronic cough in 10-20% of patients. GERD is the third cause of

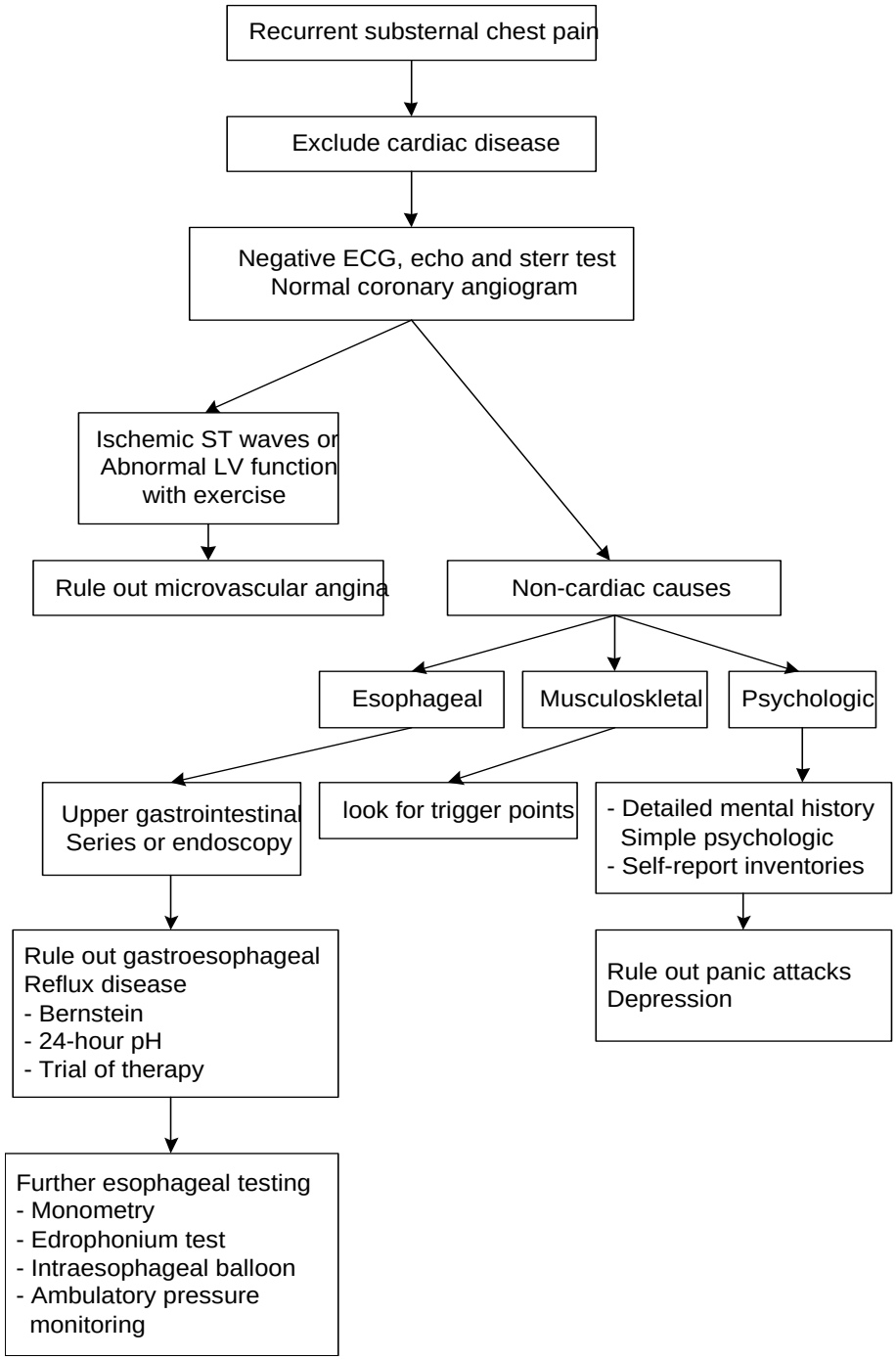

Figure 2. The algorithm of the evaluation of recurrent chest pain

chronic cough after asthma and post nasal drip.[23, 24] While Ludviksdottir found a strongly positive correlation (odds ratio = 4.4) between GERD and productive chronic cough.[25]

The pathogenesis of GERD causes asthma includes mechanosensitive (acid) afferent nerve fibers in the esophagus. In some patients, a little acid could induce bronchial spasm. GERD was found in approximately 30-90% of asthmatic patients, but a cause and effect correlation has yet to be proven.[26]

El Erag and Sonnenberg conducted a case-control study to find the correlation between asthma and esophagitis, resulting in an odds ratio of 1.51 (95% Cl, 1.43 to 1.59).[27] This data illustrate the close relationship between asthma and GERD.

Harding found a strong relationship between asthma and esophageal disturbances in the form of heartburn, regurgitation, nausea and acidic esophagus. Out of 55 asthmatic patients, 35 (64%) reported GERD symptoms, while 58 (98%) of 59 patients with chronic cough was found with GERD. In general, 119 out of 151 (78.8%) patients with respiratory tract disturbances demonstrated a relationship with esophageal acidity.[28]

Many studies have been conducted to evaluate the effect of anti-reflux therapy. From 1966 to 1999 there were 12 studies, involving 326 patients, 70% of which demonstrated improved symptoms, 62% demonstrated reduced use of asthmatic medications, and 26% demonstrated lung function improvements.[29]

Otolaryngeal disturbance

The development laryngeal manifestation in GERD are caused by the formation of singer's node, laryngitis, hoarseness, subglotic stenosis, and laryngeal malignancy. These are cause by continuous gastroesophageal reflux at night. [30]

The upper esophageal sphincter pressure is reduced at night, probably giving way for the reflux fluid to pass freely, while defense mechanisms and neutralizing agents such as saliva and cough are suppressed. The reflux material then adheres to the larynx, pharynx, or oral epithel, causing edema, inflammation and ulcer. These pathologic changes causes the disease as mentioned.[30]

GERD is the chief contribution trigger factor for asthma, as well as many complaints of the ears, nose, and throat. For example, over 80% of GERD patients suffer from difficult to manage hoarseness, while 25 to 50% of GERD patients feel the presence of a mass, and several suffer from laryngeal cancer. Clinical suspicion is the key to the diagnosis, since many patients do not complain of classic symptoms of pyrosis and regurgitation. Monitoring of the pH level of the lower and upper esophagus, pharynx, and larynx, is very helpful for establishing the diagnosis. Suppression of acid secretion using medications as well as surgical therapy would cure and aid these patients.[31] El-Seraq HB evaluated 101.366 cases of esophagitis and esophageal stricture to determine a relationship, and compared it with the incidence of sinusitis (Odds ratio 1.6 (1.51-1.7); Cl 95%), laryngitis (OD 2.01; 1.53-2.63), pharyngitis (1.48; 1.15-1.89), aphonia (1.81-2.80), laryngeal stenosis (2.02; 1.12-3.65), chronic bronchitis (1.28; 1.22-1.34), asthma (1.51; 1.43-1.59), chronic obstructive pulmonary disease (1.22; 1.16-1.27), lung fibrosis (1.36; 1.43-1.59), bronchiectasis (1.26; 1.09-1.47), and pneumonia (1.15; 1.12-1.18). We could thus conclude that GERD is a risk factor for disease of the sinus, larynx, pharynx, and lungs.[32]

Management

The physiological stimulus for gastric acid secretion is food. The secretion process is divided into three phases; the cephalic, gastric, and intestinal phases. Basal gastric acid secretion has a circadian variation, being high at night and low in the morning.[33]

A step by step approach in the management of GERD patients has been long been the rule. Initial therapy is commenced by a simple therapeutic approach. GERD management include life-style modification, avoidance of meals before bedtime, and elevating the head during sleep. Pharmacological intervention takes the form of administration of antacids, H_2-receptor antagonists (H_2Ras), prokinetic agents, and proton pump inhibitors. Surgical intervention may be taken for recurrent GERD, but such cases are rare.[34]

In the year 1987, Kruse-Anderson evaluated the acidity of GERD patients, and found reflux for 6 hours at night. Out of normal patients, 5.5% were found with reflux, while 37.9% of GERD patients were found with reflux. Esophageal motility of all patients were reduced at night.[35] Sozzi reported reduced gastric acid pH below 2 at night (from 11 pm to am).[36]

Gastric acid secretion is influenced by several factors, including histamine, acetylcholine, and gastrin. Gastrin acid production generally depends on proton pumps, influenced by the enzyme H^+/K^+ ATPase. Enzyme inhibition at the proton pumps using proton-pump inhibitor agents would not totally eliminate gastric acidity for 24 hours, even when administered day and night.[37]

Robinson compared the therapeutic effect of the administration of 20 mg of omeprazole in the morning and at night before bed (OME/OME) to the administration of 20 mg of omeprazole in the morning and 75 mg of

ranitidine at night before bed (OME/RAN). A reduction of acid release at night was found in 68.75% of the (OME/RAN) group and in 87.5% of the (OME/OME) group.[38]

Meier reported 4 out of 15 (27%) of asthmatic patients with GERD who demonstrated improved lung function (FEV1 more than or equal to 20%) after administration of 20 mg of omeprazole daily for six weeks.[39]

In GERD patients with extra-esophageal symptoms, Peghini recommends initial therapy using proton pump inhibitors twice daily (omeprazole 40-80 mg or lansoprazole 60-120 mg daily) for 3 months until symptoms subsided. It would be even better to administer H_2 inhibitors to prevent night-time acid release.[40, 41]

CONCLUSION

1. Gastroesophageal Reflux Disease (GERD) could cause or trigger non-cardiac chest pain, respiratory tract disturbances, as well as otolaryngeal disturbances.
2. The pathophysiological of GERD is through 2 chief mechanisms, through the presence of gastroesophageal reflux with or without aspiration, and through the stimulation of the esophagopulmonary reflex.
3. GERD manifestations could take the form of non-cardiac chest pain, asthma, chronic bronchitis, laryngitis, hoarseness, lung fibrosis, and malignancy.
4. Management is the same as general therapy for GERD, and is emphasized on the use of high doses of proton pump inhibitors and H_2 inhibitors at night.

REFERENCES

1. Wrigth, R.A.M.A Sagetalian, M. Esimon: Exercise induced asthma is gastroesophageal reflux a factor. Dig. Dis. 1996; 41: 921-5.
2. Field KS, M. Karaus, R Brant: Prevalence of gastroesophageal reflux symptoms in asthma CHEST 1996; 109: 316-22.
3. Lam HG Th, Deckker W, Kan G. Acute non-cardiac chest pain a coronary care unit; evaluation by 24-hour pressure and pH recording of the esophagus. Gastroenterology 1992; 102: 453-60.
4. Gregory A Bayce, H Worth Bayce Jr. Esophagus: Anatomy and structure anomalies, a text book of gastroenterology, second edition, edited by Tadataka Yamada, Philadelphia, JB Lippincott Company, 1995.p.1156-73.
5. Meyer GW, Austin RM, Brady CE. Muscle anatomy of the human esophagus. J. Clin Gastroenterol 1986; 8: 131.
6. Kitano S, Terblaance J, Kahn P. Vencus anatomy of the lower oesophagus in portal hypertension practical implications. Br. J. Surg. 1986; 73: 525.
7. Peden JK, Schneder CF, Bickel RD. Anatomic relation of the vagus nerves to the esophagus. Am. J. Surg. 1950; 80: 32.
8. Goetsch E. The structure of the mammalian oesophagus. Am. J. Anat. 1910; 10: 11.
9. Crausaz FM, Faves G. Aspiration of solid food particles into lungs of patients with gastroesophageal reflux and chronic bronchial disease. Chest 1988; 93: 376-8.
10. Tuchman DN, Doyle JT, Pack Al, Schwartz J, Kokonos M, Spitzer AR. Comparison of air way responses following tracheal or esophageal acidification in the eat. Gastroenterology 1984; 87: 1712-5.
11. Richter JE. Approach to the patient with non-cardiac chest pain. Text book of gastroenterology, second edition edited by Tadataka Yamada, Philadelphia, JB Lippincott company, 1995.p.29: 648-70.
12. Gostal OL, Castell JA, Castell DO. Frequency and site of gasteroesophageal reflex in patients with chest symptoms. Chest 1994; 106: 1793-96.
13. Hewson EG, Sinclair JW, Dalton CB, Richter JE. 24-hour esophageal pH monitoring. The most usefull test for evaluating non-cardiac chest pain. Am J Med. 1991; 90: 576.
14. De Meester TR, O'Sillivan GC, Bermudez G. Esophageal function in patients with angina type chest pain and normal coronary angiogram. Ann Surg. 1982; 196: 488.
15. De Caestecker JS, Brown J, Bladewell JX, Heading RC. The oesophagus as a cause of recurrent chest pain: which patients should be used? Lancet 1985; 2: 1143.
16. Schofield PM, Bennett DH, Whorwell PJ. Exertional gastroesophageal reflex: a mechanism for symptoms in patients with angina pectoris and normal coronary angiograms. Br Med J. 1987; 294: 1459.
17. Singh S, Richter JE, Hewson EG, Siclair JW, Hawkshaw BT. The contribution of gastroesophageal reflux to chest pain in patients with coronary artery disease. Ann. Intern Med. 1992; 117: 824.
18. Alban-Davies H, Jones DB, Rhodes J. Angina-like esophageal chest pain: differentiation from cardiac pain by history. J Clin Gastroenterol 1986; 7: 477-81.
19. Fennerty MB. Extraesophageal GERD: Presentations and approach to treatment. GI in the next century, clinical advances in esophageal and gastrointestinal disorder. AGA Postgraduate Course, Orlando, Florida. 1999: 1 – 10.
20. Fass R, Fennerty MB, Ofman JJ. The clinical and economic value of a short course of omeprazole in patients with non-cardiac chest pain. Gastroenterology 1998; 115: 42-9.
21. Karlsson J-A, Sant'Ambrogio G, Widdicombe J, Afferent neural pathways in cough and reflex bronchocontriction. J Appl Physio 1988; 65: 1007-23.
22. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann Intern Med 1992; 117: 234-42.
23. Irwin RS, Boulet LP, Cloutier MM. Managing cough as a defense mechanism and as a symptoms – A consensus panel report of the American college of chest physicians. Chest 1998; 114: S 133-81.
24. Symptom NA, Irwin RS, Curley FJ. From a propective study of chronic cough: Diagnostic and therapeutic aspects in older adults. Arch Intern Med 1988; 158: 1222-8.
25. Ludviksdottir D, Bjornsson E, Janson C, Bornan G. Habitual coughing and its associations with asthma, anxiety and gastroesophageal reflux. CHEST. 1996; 109: 1262-7.
26. Sontag SJ. Gastroesophageal reflux and asthma. Am J Med 1997;

103: 84S-90. Sontag SJ, O'Connell S, Khandelwal S. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99: 613-20.
27. El Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United State military veterans. Gastroenterology 1997; 113: 755-60.
28. Harding SM, Guzzo MR, Richter JE. 24-h Esophageal pH Testing in Asthmatics: Respiratory symptom correlation with esophageal acid events. CHEST 1999; 115: 654-9.
29. Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatic with gastrophageal reflux? A critical review of the literature. CHEST 1998; 114: 275-83.
30. Klinkenberg-Knol EC. Otolaryngologic manifestations of gastroesophageal reflux disease. Scand J Gastroenterol 1998; 33: Suppl 225: 24-8.
31. Richter JE. Extraesophageal presentation of gastroesophageal reflux disease. Semin Gastrointest Dis, 1997; 8: 75-89.
32. El-Seraq HB, Sonnerberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United State military veterans. Gastroenterology 1997; 113: 275-60.
33. Moore JCT, Wolfe M. The relation of plasma gastrin to circadian rhythm of gastric acid secretion in man. Digestion 1974; 9: 97.
34. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Arch Intern Med. 1995; 155: 2165-73.
35. Kruse-Anderson S, Wallin L, Madsen T. Acid gastryesophageal reflux and oesophageal pressure activity during postprandial and nocturnal periods: a study in subjects with and without pathologic acid gastroesophageal reflux. Scand J Gastroenterol. 1987; 22: 926-30.
36. Sozzi M, Valentini M, Bertolissi E, Serraino D, Bovero E, Delaco F. Nocturnal gastric acidity pattern in gastro-oesophageal reflux disease with or without oesophagitis. Ital j Gastroenterol. 1995; 27: 413-8.
37. Hendel J, Hendel L, Aggestrup S. Morning or evening dosage of omeprazole for gastro-oesophageal reflux disease? Aliment Pharmacol Ther, 1995; 9: 693-7.
38. Robinson M, Rodriquez-Stanley S, Gardner JD. In GERD patients taking a morning deso of omeprazole , bedtime low-dose ranitidine is equivalent to bedtime omeprazole for inhibition of nocturnal gastric acidity. Gastroenterology 2000; 118.
39. Meier MJH, McNally PR, Punja M, Freeman SR, Sudduth RH, Stocker N, et al. Does omeprazole improve respiratory function in asthmatic with gastroesophageal reflux? Digestive Disease and Sciences, 1994; 39: 2127-33.
40. Peghini PL, Katz PO, Bracy NA. Nocturnal recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. Am j Gastro 1998; 93: 763-7.
41. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. Gastroenterology 1998; 115: 1335-9.