The Role of Esophageal pH-metri Test on Gastro-Esophageal Reflux Disease Diagnosis

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ABSTRACT

Gastro-esophageal reflux disease is a pathological condition of esophagus which is caused by gastric content reflux into esophagus. There is an increased prevalence of gastro-esophageal reflux disease. The roles of esophageal pH-metry in clinical application include looking for abnormal acid exposure on esophagus with no abnormality found in endoscopy; evaluating patients following the anti-reflux surgery who are being suspected for abnormal esophageal reflux; evaluating patients with normal endoscopic result but still having refractory reflux symptoms against proton pump inhibitor medication; detecting refractory reflux in patients chest pain following the heart evaluation; evaluating patients with otolaryngologic manifestations (laryngitis, pharyngitis, chronic cough) of the esophageal reflux disease after therapeutic failure of 4-weeks proton pump inhibitor treatment; and looking for correlation between adult onset gastro-esophageal reflux disease and non-allergic asthma.

***Keywords**: gastro-esophageal reflux disease, esophagus pH-metry, symptoms-reflux correlation*

INTRODUCTION

Gastro-Esophageal Reflux Disease (GERD) is a pathological condition of esophagus which is caused by gastric content reflux into esophagus. The typical symptom is burning sensation in chest area, but it can also come with other symptoms such as regurgitation (sour and bitter taste in tongue), epigastric pain, dysphagia or odinophagia.[1]

The prevalence of gastro-esophageal reflux disease is quite high. In western countries, the prevalence is 10-20%, but in Asia the prevalence is only 3-5%, except in Japan 13-15% and in Taiwan approximately 15%.[2] In 1998, Syafruddin reported a study in patients with dyspeptic symptoms who underwent endoscopy in Cipto Mangunkusumo hospital; esophagitis was found in 22.8% of them.[3] Syam et al reported that among 1,718 patients in Cipto Mangunkusumo Hospital who underwent upper gastrointestinal tract endoscopy based on dyspepsia indication in 5 year time (1997-2002), there was an increase in esophagistis prevalence from 5.7 in 1997 into 25.18% in 2002 (mean 13.13%). In the United States, the prevalence of gastro-esophageal reflux disease increases significantly, almost 25% of population experiences GERD.[4]

Gastro-esophageal reflux disease is by with esophagitis appearance with or without mucosal break. Confirmed diagnosis of esophagitis reflux disease is established by histopathological examination of esophageal tissue.[1] Upper gastro-intestinal tract endoscopy has low sensitivity in diagnosing GERD. Abnormal esophageal mucosa is not found in approximately 50% patients who undergo endoscopy. Endoscopy is the gold standard for diagnosing erosive esophagitis, Barrett's esophagus, esophageal stricture and adenocarcinoma.[5] Twenty-four-hour esophageal pH monitoring test is the gold standard diagnostic test to assess gastric acid reflux into esophagus.[7-10]

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DEFINITION

Gastro-esophageal reflux disease is a pathological condition which is caused by gastric content reflux through incompetent gastro-esophageal junction causing trauma and inflammation on esophageal mucosa. Gastro-esophageal reflux disease can be categorized into three distinct groups, which are Non-Erosive Reflux Disease (NERD), erosive esophagitis and Barrett's esophagus. NERD is defined with the presence of typical symptoms of gastro-esophageal reflux disease which is caused by intra-esophageal gastric content but no abnormal esophageal mucosa is not found on endoscopy.[5,6]

International workshop group (World Congress of Gastroenterology in Los Angeles 1994) stated the presence of mucosal break as a diagnosis of erosive esophagitis. It also categorized the degree of esophagitis into four stages according to the extent of esophagitis (table 1).[5,11]

Table 1. Los Angeles Classification on the degree of esophagitis.[5,11]

Damage degree	Endoscopic features
A	Small erosion on esophageal mucosa with diameter < 5 mm
B	Erosion on esophageal mucosa/fold with diameter > 5 mm which are not connected to one another
C	Confluent lesions which are not in contact/encircling the whole lumen (< 75%)
D	Esophageal mucosa lesion which encircles at least 75% of the whole lumen (encircling the whole esophageal lumen)

According to the recent guideline from American College of Gastroenterology, Barrett's esophagus is defined as esophageal epithelial alteration with different length which can be recognized during endoscopy and is confirmed by intestinal metaplasia, which is found inn esophageal biopsy result.[5]

PATHOGENESIS

Esophagitis on GERD will occur if there is a contact between refluxate material and esophageal mucosa for long period of time, also if there is a decrease in mucosal resistance or esophageal tissue protection setting off trauma and inflammation on esophageal mucosa which will cause GERD signs and symptoms to appear. Thus, it can be stated that pathogenesis of GERD associates with the imbalance between defensive factors of esophageal mucosa and aggressive factors of refluxate material which are originated from stomach, where there is shortcoming in defensive factor compared to its aggressive factor.[11-13] GERD occur due to various factors, e.g. because of:[3,6,11-14] (1) Incompetent Lower Esophageal Sphincter (LES). LES can be caused by hiatus hernia, LES total length, drugs (anti-cholinergic, beta adrenergic antagonist, theophylline, benzodiazepine, calcium channel blocker, opiates), hormonal factors (pregnancy, elevated progesterone, cholecystokinine, secretine level); (2) Transient Lower Esophageal Sphincter Relaxation (TLESR). There is spontaneous LES relaxation which lasts for 5 seconds without preceding swallowing process. GERD with normal LES is mostly caused by transient LES relaxation; (3) Decreased or delayed acid clearance from esophagus. There are 4 types of clearance process from normal esophagus including gravitational force, peristaltic force, salivation and formation of intrinsic bicarbonate by esophagus. Night time reflux cannot be overcome because the absence of gravitational force and saliva, and the peristaltic process does not

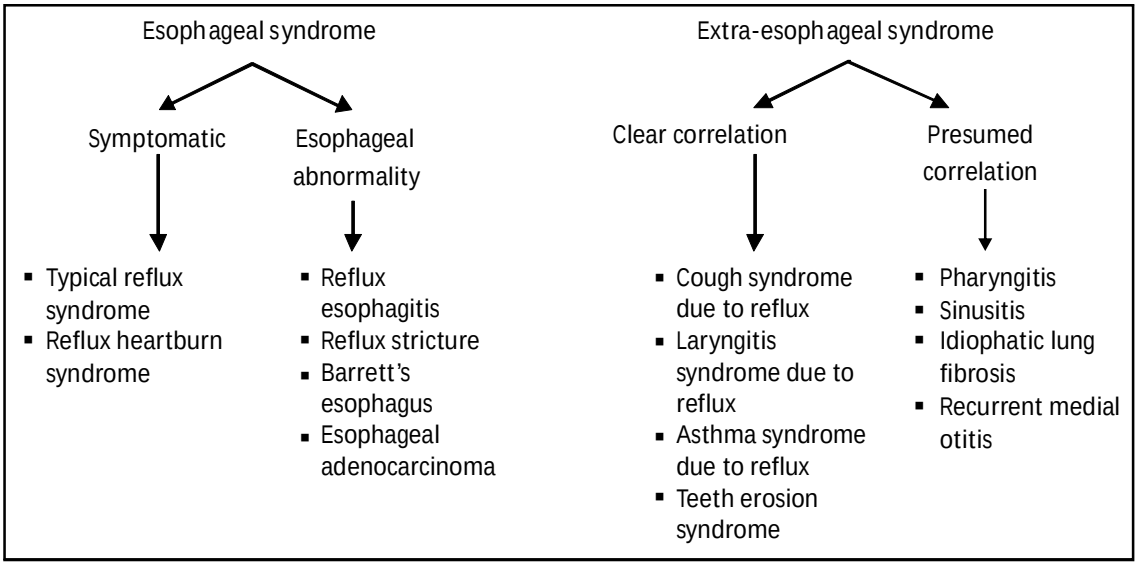

Figure 1. Symptoms and complication of gastro-esophageal reflux disease.[18]

function; (4) Gastric abnormality which increases physiological reflux, e.g. gastric dilatation, pylorus obstruction and delayed gastric emptying; (5) Decreased epithelial mucosa resistance; (6) Chemical composition of refluxate fluid, whether it is only composed of gastric acid, pepsin or duodenal/biliary fluid. Certain food, such as lime juice, tomatoes and coffee, increases the symptoms of GERD patients.

Patients usually complain of epigastric, retrosternal or lower chest discomfort. Such discomfort commonly manifest into heartburn, dysphagia, nausea or regurgitation. Patients sometime have complaints of sour or bitter taste on tongue or hyper-salivation. Heartburn sensation can sometime be found in healthy persons; however, if it happens every day and repeatedly, it has diagnostic prediction value of 60%. Heartburn predominantly occurs at night or after meal. This complaint becomes exaggerated during bending position or after consuming alcoholic beverage, fruit juice, coffee, and hot or cold beverage. This disease can cause several complications, such as stricture (10%), bleeding (rare), Barrett's esophagus (12.4%), esophageal cancer or esophagus adenocarcinoma (10%). In addition to esophageal abnormality, extra-esophageal complications may occur, such as laryngitis, bronchitis, bronchiectasis or asthma.[12,13,15-19]

DIAGNOSIS

Technical Aspect of Esophageal pH-metryTest

Basic equipments for esophageal pH-metry test are portable data loggers, pH electrode, computer and software to analyze pH data.[20] Electrode is inserted through the nostril down to 5 cm above the upper rim of Lower Esophageal Sphincter (LES). This 5 cm length is to prevent electrode displacement into the stomach when esophagus contract during swallowing process. Extremely high electrode placement above LES may decrease this test sensitivity.[20,21]

Original evaluation system according to Johnson and DeMeester evaluates 6 variables, i.e: (1) total percentage of time when pH < 4 (normal < 4.2); (2) pH percentage < 4 during standing position (normal < 6.3); (3) pH percentage < 4 during prone position (normal < 1.2); (4) the number of reflux episode (normal < 50); (5) the number of reflux episode with pH < 4 for ≥ 5 minutes (normal three times or less); (6) the longest single acid exposure episode period (normal 9.2). [10,20,22] According to consensus total percentage of time of pH < 4 (the period of acid exposure on esophagus) is the most distinguishing factor between physiological and pathological reflux.[20]

Interpretation Technique and Normal Value of Esophageal pH-metry

Esophageal reflux is a physiological phenomenon in normal individual. The aim of esophageal pH monitoring is to identify patients with GERD by demonstrating reflux pathologic degree. Besides being influenced by acid exposure period in patients with GERD, the factors that can differentiate GERD patient from control are acid sensitivity of esophageal mucosa, mucosal resistance to inflammation, the extent of mucosa exposed to acid, or the composition of refluxate fluid other than acid.

Acid Exposure on Esophagus in Normal Control versus Esophagitis

In accordance with a study shown on table 2, comparing acid exposure period on esophagus in normal persons and esophagitis patients, sensitivity of 77-100% and specificity of 85-100% are found. Although table 2 only shows pH < 4 percentage data, but other parameters show similar result.[20]

Acid Exposure on Esophagus in Normal Control versus GERD patients with negative Gastro-Duodenal Endoscopy

Heartburn and acid regurgitation are typical reflux symptoms which occur in 40% normal population have not received treatment. According to studies on table 3, the "normal" criteria being used on pH monitoring data analysis varies among studies. Subjects with negative endoscopy result show that the mean value of acid exposure is slightly above normal.[20]

Table 2. Acid exposure on esophagus in patients with esophagitis[20,22,23]

Reference	Control		Patient with esophagitis		Sensitivity and specificity
	Upper limit of normal percent pH < 4	n	Range of mean age (year)	Mean percent pH < 4	
Vitale et al	7.2	35	51 (20-82)	9.6	77% and 91%
Schindlbeck et al	7.0	16	47 (18-73)	18.8	89% and 93%
Johnssson et al	3.4	20	51 (28-74)	Not stated	87% and 97%
Mattioli et al	5.0	11	48 (21-78)	29.8	100% and 100% (grade 2)
		37		27.6	92% and 100% (grade 3)
Masclee et al	4	44	48	12.6	91% and 85%
Kapasidis et al	3.9	21	37	31.7	Not provided

Table 3. Acid exposure on esophagus in GERD patients with negative endoscopy result.[20,22,23]

Reference	Upper limit of normal percent pH < 4	Patient with GERD		Sensitivity and specificity
		n	Mean percent pH < 4	
Vitale et al	7.2	11	5.8	64% and 91%
Schindlbeck et al	7.0	29	10.2	Not provided
Mattioli et al	5.0	6	1.9	0% and 100% (grade 0)
		32	13.6	71% and 100% (grade 1)
Masclee et al	4	23	6.4	61% and 85%
Kapasidis et al	3.9	21	11.6	Not provided

Reflux-symptoms Correlation

In accordance with facts, a significant reflux event may cause atypical symptom (chest pain); therefore, 24-hour-pH data analysis associated with symptoms is carried out to the patients by marking the events. To determine a significant pain-reflux association, we can use:[20,21] (1) Symptom Index (SI): is defined as the number of symptoms episode associated with reflux (pH < 4) divided by the number of symptoms episode (in percentage). This formula has limitation of not being able to calculate the number of total reflux episode; (2) Symptom Sensitivity Index (SSI): is a percentage of symptoms correlated to reflux episode divided by the number of total reflux episode. This system is also limited and incapable to calculate the number of total symptom episode; (3) Symptom Association Probability (SAP): is calculated by using contingency table which comprises of four parts: (a) positive symptom, positive reflux: (b) negative symptom, positive reflux; (c) positive symptom, negative reflux; and (d) negative symptom, negative reflux. Fisher's exact test is used to calculate probability of correlation between reflux and symptom occurrence. SAP value > 95% indicates that the probability of correlation between reflux and symptom by chance is < 5%.

CLINICAL APPLICATION

The Application of 24-hour Esophageal pH-metri

The 24-hour esophageal pH-metry is very beneficial in diagnosing and managing patients with esophageal syndrome, including gastro-esophageal reflux, extra-esophageal manifestation or chest pain. The roles of 24 hour esophageal pH-metry are: (1) to look for abnormal acid exposure on esophagus, which has no abnormality found on endoscopy, (2) to evaluate patients following the anti-reflux surgery who are being suspected to have abnormal esophageal reflux, (3) to evaluate patients with normal endoscopic result but still having refractory reflux symptoms against proton pump inhibitor medication; (4) to detect refractory reflux in patients with chest pain following the heart evaluation; (5) to evaluate patients with otolaryngologic manifestations (laryngitis, pharyngitis, chronic cough) of esophageal reflux disease after therapeutic failure of 4-week proton pump inhibitor treatment; (6) to look for the correlation between adult onset gastro-esophageal reflux disease and non-allergic asthma.[20]

Typical Gastro-esophageal Reflux Disease

Reflux test is generally not indicated for the majority of GERD patients with noticeable improving symptoms due to medical treatment. Patients with reflux complication, such as erosive esophagitis, peptic stricture or Barrett's esophagus, do not need pH test to confirm the diagnosis. The first indication is to document abnormal acid reflux prior to surgical treatment or GERD endoscopy or for GERD treatment research purpose.[20,21,24]

Several studies show that esophageal pH test is more sensitive in patients with erosive esophagitis compared to non-erosive reflux. The severity of erosive esophagitis has positive correlation with acid exposure on distal esophagus.[25-27]

The second indication in GERD patients is to monitor adequate reflux control following medical treatment in asymptomatic patients with complication. High degree of acid exposure on distal esophagus is correlated to the length part of Barrett's esophagus. Some studies prove that patients with Barrett's esophagus fail to normalize acid on distal esophagus even they are being under PPI treatment. In this particular case, there is a confounder. Patients with Barrett's esophagus have decreased sensitivity to acid reflux events, thus they do not realize reflux occurence.[28]

Refractory Chest Pain

Esophageal pH monitoring is generally used to evaluate patients with persistent reflux symptoms, regardless of having received therapy or surgery. In these patients, several tests are being done, including pH monitoring, biliary reflux detection, or impedance monitoring to differentiate reflux symptom associated with inadequate GERD treatment or its etiology is not associated with GERD. In such case, endoscopic detection on distal erosive esophagitis is not specific and not sensitive.[21,29]

Refractory heartburn is defined as heartburn which is irresponsive to acid suppression therapy. Although

PPI therapy is perceived as the best therapeutic agent up to now, but the dose and time of PPI therapy on failure cases has not been studied. There is significant abnormal acid exposure in patients with severe erosive esophagitis degree, although they have been treated with PPI therapy.[21]

There are three common points that need to be observed by using pH test in patients with refractory reflux symptom who are under treatment, i.e.: (1) Abnormal acid exposure on esophagus frequently occurs in patients who have once daily PPI therapy with typical and atypical reflux symptom; (2) Patients with greater reflux complication - including greater esophagitis severity degree and Barrett's esophagitis – have lower pH normalization regardless of twice daily PPI therapy; (3) Diagnosis with pH test in refractory patients yields more representative result in patients with typical reflux symptom than in patients with extra-esophageal symptom. [21]

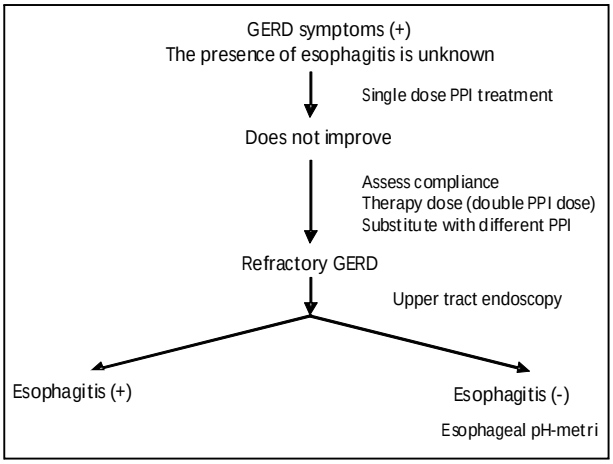

Figure 2. Algorithm of refractory GERD evaluation.[29]

Chest Pain

Approximately 30% patients with recurrent chest pain have normal coronary arteriography. Chest pain associates with GERD, which is similar to angina pectoris symptom. Abnormal esophageal pH is found in approximately 60% patients with non-cardiac chest pain, either in the form of both abnormal acid exposure and/or associated with reflux symptom.[20,21,24]

Empirical test with high-dose PPI is one of options for diagnosing GERD in patients with non-cardiac chest pain. Twenty-four-hour pH monitoring is performed if patients do not respond to high-dose PPI. Acid reflux can be excluded as the cause of non-cardiac chest pain in patients with recurrent chest pain episode - regardless whether they are having therapy or not -and in patients with normal pH test result. pH analysis has to be combined with reflux symptom correlation calculation for patients with chest pain symptom and persistent reflux on PPI therapy.[13,20,21]

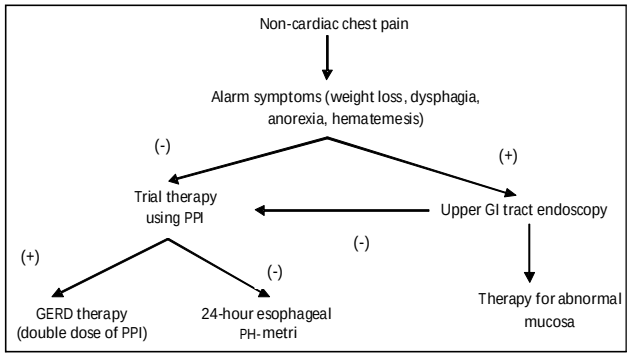

Figure 3. Algorithm of management for patients with non-cardiac chest pain.[19]

Chronic Laryngeal Symptom

Patients with dominant symptoms such as chronic cough, hoarse voice, globus, sore throat and excessive throat clearing are often diagnosed as GERD after laryngoscopy procedure. Twenty-four-hour pH monitoring is frequently performed following endoscopy if esophagitis is not found. Prevalence prior to therapy in abnormal pH test is reported to be 53%, with acid exposure prevalence on distal, proximal and hypo-pharynx of 42%, 44% and 38%, respectively.[21]

As in non-cardiac chest pain, practical and popular approach is by means of empirical test with twice daily PPI regimen for several months; pH test is reserved for patients with persistent symptom. Application of pH test result is limited in clinical setting. Charbel et al reported that out of 115 patients with extra-esophageal symptom who have twice daily PPI regimen, abnormal acid reflux result was only found in 1% of them.[30]

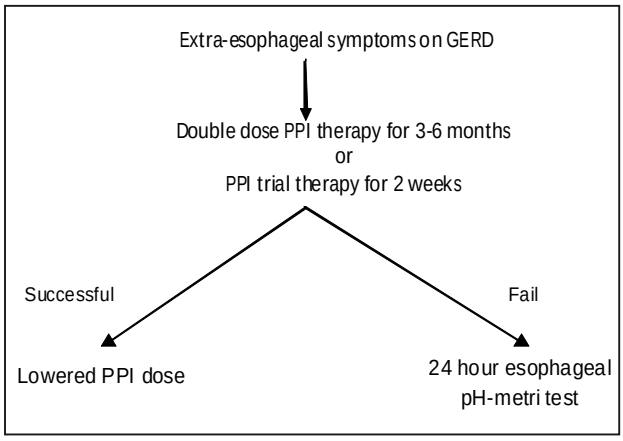

Figure 4. Evaluation for GERD patients with extra-esophageal symptom.[19]

Asthma

GERD prevalence in asthmatic patient ranges from 34% to 89%. Abnormal acid reflux result is often found in asthmatic patients without reflux symptom (silent refluxers). The role of esophageal pH monitoring is

still unknown in asthmatic patients. Although according to latest study, abnormal pH test prevalence reaches 66%, this test cannot determine whether this acid reflux causes asthma or GERD induces asthma attack.[31]

As in patients with extraesophageal symptom, most patients with suspected asthma on GERD do not need preliminary esophageal pH test. Acid suppression empiric test with double dose of PPI treatment followed with 24-hour pH monitoring in irresponsive patients is the most cost-effective diagnostic test to determine GERD that aggravates asthma.[32]

CONCLUSION

Gastro-esophageal reflux disease is a pathological condition on esophagus which is caused by gastric content reflux into esophagus. There is increased prevalence of gastro-esophageal reflux. Esophagitis on GERD occurs if there is a contact between refluxate material and esophageal mucosa for long period of time, also if there is a decrease in mucosal resistance or esophageal tissue protection setting off trauma and inflammation on esophageal mucosa.

Esophageal pH monitoring is indicated to look for acid exposure on abnormal esophagus with no abnormality found in endoscopy, to evaluate patients following the antireflux surgery who are being s uspected for abnormal esophageal reflux, to evaluate patients with normal endoscopic result but still having refractory reflux symptoms against proton pump inhibitor medication, to detect refractory reflux in patients with chest pain following the heart evaluation, to evaluate patients with otolaryngologic manifestations (laryngitis, pharyngitis, chronic cough) of esophageal reflux disease after therapeutic failure of 4-week proton pump inhibitor treatment, to look for the correlation between adult onset gastro-esophageal reflux disease and non-allergic asthma.

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