THE UTILITY OF NARROW BAND IMAGING IN IMPROVING THE ENDOSCOPIC DIAGNOSIS OF OESPHAGEAL DISEASE

Thesis

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INTRODUCTION

Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms, with or without mucosal damage, and/or complications ***(Vakil et al., 2006)***

GERD is common and the prevalence(as defined by at least weekly heartburn and/or acid regurgitation)is estimated to range from 10 to 20% in Western countries and is about 5% in Asian countries ***(Moayyedi and Talley, 2006)***.

Based on clinical history and upper endoscopy findings, patients with GERD are typically classified into: non erosive reflux disease (NERD), erosive esophagitis and Barrett's esophagus (BE) ***(Mitchell and Enns, 2009).***

NERD is a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy ***(Modlin et al., 2009).***

A variety of novel endoscopic and biopsy-based methods have been evaluated in NERD in an attempt to detect subtle mucosal abnormalities that cannot be seen with standard white light imaging ***(Edebo et al., 2007).***

Histological findings have also been addressed in NERD. These include basal zone hyperplasia, papillary elongation, inflammatory infiltrates and dilated intercellular spaces. ***(Vieth, 2008).***

Narrow-band imaging (NBI) is a novel endoscopic technique that may enhance the accuracy of diagnosis by using narrow-bandwidth filters in a red-green-blue (R/G/B) sequential illumination system. Magnifying endoscopy by using NBI has two distinct applications: the analysis of the surface architecture of the epithelium (pit pattern) and the analysis of the vascular network. This new technique allows a better characterization of distinct types of gastrointestinal epithelia, as well as the disorganization of the vascular pattern in inflammatory disorders and the irregular pit pattern in early neoplastic lesions of the esophagus, stomach and large bowel ***(Gheorghe, 2006).***

In endoscopic examination, lesions are identified by changes in color and irregularity of surface mucosa. It has been postulated that NBI may lead to the same contrast enhancement capabilities as chromoendoscopy, but without using dye agents ***(Gheorghe, 2006).***

To date the research performed concerning the use of NBI endoscopy in GERD is relatively new and there is still a

need for prospective randomized controlled trials to validate the mucosal and vascular patterns. Furthermore, additional research is needed to fully assess the clinical utility of NBI not only in the diagnosis of GERD compared with conventional endoscopy, but also how it will possibly change the management of patients if they are diagnosed with mild erosive disease ***(Mitchell and Enns, 2009).***

AIM OF THE WORK

The aim of this study is to compare the accuracy of NBI endoscopy in diagnosing nonmalignant esophageal disease with conventional endoscopy and histopathological examination.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Introduction:

Gastroesophageal reflux disease (GERD) is present when passage of gastric contents into the esophagus causes troublesome symptoms or complications. The passage of gastric contents into the esophagus is a normal physiologic process that occurs in healthy infants, children, and adults. Most episodes are brief and do not cause symptoms, esophageal injury, or other complications. In contrast, gastroesophageal reflux disease (GERD) is present when the reflux episodes are associated with troublesome symptoms or complications ***(Vandenplas et al., 2009)***

Physiologic reflux episodes typically occur post prandially, are short-lived, asymptomatic, and rarely occur during sleep. Pathologic reflux is associated with symptoms or mucosal injury, often including nocturnal episodes. In general terms, gastroesophageal reflux disease (GERD) is applied to patients with symptoms suggestive of reflux or complications but not necessarily with esophageal inflammation. Reflux esophagitis describes a subset of patients with symptoms of GERD who also have endoscopic or histopathologic evidence of esophageal inflammation ***(Kahrilas et al., 2013).***

Due to the broad spectrum of conditions attributable to reflux, there is little agreement as to what constitutes typical reflux disease. A consensus statement (the Montreal Classification) definesGERD as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. According to the Montreal Working Group, heartburn is considered troublesome if mild symptoms occur two or more days a week, or moderate to severe symptoms occur more than one day a week***(Vakil et al., 2006).***

Epidemiology:

There are limitations in the epidemiologic estimates of the prevalence of gastroesophageal reflux disease (GERD) as they are based upon the assumption that heartburn and/or regurgitation are the only indicators of the disease ***(Camilleri et al., 2005)***.

However, patients with objective evidence of GERD (such as esophagitis or Barrett's esophagus) do not always have heartburn and heartburn is not always indicative of GERD ***(Zagari et al., 2008)***.

GERD prevalence was found to be 10 to 20 percent in the Western world and less than 5 percent in Asia. The incidence in the Western world was approximately 5 per 1000 person-years. In a subsequent population-based survey in the United States,

22 percent of respondents reported that they had heartburn or regurgitation within the last month while 16 percent reported regurgitation. Heartburn or regurgitation was "clinically significant" (≥twice weekly) in 6 and 3 percent, respectively ***(Kahrilas et al., 2013)***

A large community-based study documented prevalence rates of 1.8 to 8.2 percent for symptoms associated with gastroesophageal reflux. Among adolescents, 3 to 5 percent complained of heartburn or epigastric pain, and 1 to 2 percent used antacids or acid-suppressing medication. ***(Nelson et al., 2000)***.

Pathophysiology:

Mechanisms of reflux:

The primary event in the pathogenesis of gastroesophageal reflux disease (GERD) is movement of gastric juice from the stomach into the esophagus. The anti-reflux barrier at the gastroesophageal junction is anatomically and physiologically complex and vulnerable to several potential mechanisms of reflux. The three dominant pathophysiologic mechanisms causing gastroesophageal junction incompetence are:

- Transient lower esophageal sphincter relaxations (tLESRs)
- A hypotensive lower esophageal sphincter (LES)

- Anatomic disruption of the gastroesophageal junction,often associated with a hiatus hernia.

The evolving concept is that the dominant mechanism varies as a function of disease severity with tLESRs predominating with mild disease and mechanisms associated with a hiatus hernia and/or a weak sphincter predominating with more severe disease. The relatively recent availability of esophageal impedance testing, which can detect reflux irrespective of pH, discern reflux of gas from liquid, and determine the distribution of refluxate, will likely help determine the impact of these variables on the clinical features of GERD***(Kahrilas et al., 2013).***

Transient lower esophageal sphincter relaxations:

Transient lower esophageal sphincter relaxations account for essentially all reflux events in individuals with a normal LES pressure at the time of reflux. There are several major differences between tLESRs and swallow-induced LES relaxation: tLESRs occur without an associated pharyngeal contraction, are unaccompanied by esophageal peristalsis, and persist for longer periods (>10 sec) than do swallow-induced LES relaxations ***(Modlin et al., 2009).***

It has become increasingly clear that tLESRs are the physiological mechanism of belching. The frequency of tLESRs is greatly increased by distension of the stomach or by

assuming an upright posture. Furthermore, a tLESR is an integrated motor response involving not only LES relaxation, but also crural diaphragmatic inhibition, esophageal shortening by contraction of its longitudinal muscle, and contraction of the costal diaphragm. That tLESRs are an active, vagaly mediated reflex, rather than the result of forceful gastric distention, was demonstrated by both a combined endoscopic/manometric study and a combined manometric/fluoroscopic study showing that sphincter relaxation (evident manometrically) always preceded actual esophagogastric junction opening ***(Massey et al., 2006)***.

One hypothesis is that a primary determinant of reflux disease is not an increased number of tLESRs, rather an increased proportion of tLESRs that are associated with acid reflux as opposed to only gas venting. Such a progression could be caused by increased compliance of the EGJ as a consequence of weakening/dilatation of the diaphragmatic hiatus. Increased compliance leads to an increased luminal cross-sectional area during opening that in turn results in an increased volume of reflux and a reduced ability to limit refluxate to gas. Different investigators have documented acid reflux during as many as 93 percent or as few as 9 to 15 percent of tLESRs ***(Pandolfinoet al., 2006)***.

Hypotensive lower esophageal sphincter:

The LES is a 3 to 4 cm long segment of tonically contracted smooth muscle at the distal end of the esophagus. LES tonic contraction is a property of both the muscle itself and of its extrinsic innervation. Normal resting tone of the LES varies from 10 to 30 mmHg, being greatest at night ***(Kahrilas et al., 2013)***.

Only a minority of individuals with GERD have a grossly hypotensive LES (<10 mmHg) when determined during fasting measurements. There are, however, a host of factors that can reduce LES pressure: gastric distension, cholecystokinin, various foods (fat, chocolate, caffeine, alcohol), smoking, and many drugs. Thus, many patients have periods of gross LES hypotension as a result of foods, drugs, or habits ***(Wu et al., 2007).***

Gastroesophageal reflux can occur with diminished LES pressure either by strain-induced reflux or free reflux:

- Strain-induced reflux occurs when a hypotensive LES is overcome and "blown open" by an abrupt increase of intraabdominal pressure. Manometric data suggest that stress reflux is relatively unusual unless the LES pressure is less than 4 mmHg. However, these studies were somewhat limited by the required instrumentation and may not be entirely reflective of normal ambulatory circumstances.

- During free reflux a fall in intraesophageal pH occurs without identifiable change in either intragastric or LES pressure. Free reflux is observed only when LES pressure is within 0 to 4 mmHg of intragastric pressure***(Kahrilas et al., 2013)***.

Hiatal hernia and the diaphragmatic sphincter:

The diaphragm as well as the LES contributes to gastroesophageal sphincter competence, making it more accurate to think of the composite as esophagogastric junction (EGJ) pressure. Recordings of LES pressure usually exhibit inspiratory increases as a result of contraction of the diaphragmatic crus that encircles the LES. Observations of the antireflux mechanism during maneuvers such as leg raising and abdominal compression suggest a "pinchcock" effect of crural contraction that augments the antireflux barrier. The crural diaphragmatic component of EGJ pressure is most relevant in patients with hiatus hernia, in whom this component may be impaired***(Kahrilas et al., 2013)***.

However, a study examining the correlation between GERD, hiatus hernia, LES pressure, and crural diaphragm function as quantified by the magnitude of EGJ pressure augmentation during inspiration found that function of the crural diaphragm was most strongly correlated with GERD. Furthermore, the associations between GERD and hiatus hernia or LES pressure no longer achieved statistical significance after considering the effect of inspiratory augmentation in multivariate analysis, suggesting both

effects were largely mediated by associated crural diaphragm dysfunction ***(Pandolfino et al., 2007)***.

Obesity:

Obesity is a risk factor for GERD, erosive esophagitis, and esophageal adenocarcinoma. The mechanisms by which this occurs are incompletely understood.***(Kahrilas et al., 2013)***.

Several studies have evaluated the relationship between obesity and GERD but comparison among them is limited by variable definitions used and differences in study design***(Corley and Kubo, 2007)***.

One of the most comprehensive studies included a total of 285 patients in whom anthropometric variables were correlated with findings on manometry ***(Pandolfino et al., 2006)***.

There was a significant correlation of body mass index and waist circumference with intragastric pressure and the gastroesophageal pressure gradient. Obesity was also associated with disruption of the esophagogastric junction leading to a hiatal hernia and increased esophageal acid exposure***(De Vries et al., 2008).***

Obesity, particularly abdominal obesity, has also been associated with increased reflux symptoms***(Corley et al., 2007).***

Extending on these findings, another report found obesity to be associated with both an increased frequency of tLESRs and an increased proportion of tLESRs associated with acid reflux during the postprandial period in subjects without hiatus hernia or clinical evidence of GERD. These findings suggest that LES dysfunction might be an important mediator of the pathogenesis of obesity-related GERD ***(Wu et al., 2007).***

Whether weight loss can reverse obesity-related changes is unclear. In a study involving questionnaires obtained from 10, 545 women, body mass index was associated with symptoms of GERD in a dose-response relationship. Even moderate weight gain in women of normal weight was potentially associated with exacerbation of symptoms***(Jacobson et al., 2006)***

Esophageal acid clearance:

Following reflux, the period that the esophageal pH remains less than 4 is called the acid clearance time. Esophageal acid clearance begins with emptying the refluxed fluid from the esophagus by peristalsis and is completed by titration of the residual acid by swallowed saliva. Approximately 7 mL of saliva will neutralize 1 mL of 0.1 Na HCl, with 50 percent of the neutralizing capacity being attributable to salivary bicarbonate. The normal rate of salivation is about 0.5 mL/min; maneuvers that increase salivation (e.g, oral lozenges or gum chewing) will hasten

acid clearance while circumstances of diminished salivation (e.g, sleep) will delay it ***(Kahrilas et al., 2013).***

Prolongation of esophageal acid clearance occurs in about one-half of patients with esophagitis. A review of a large data set of 24-hour esophageal pH recordings suggested that individuals with known hiatus hernias tended to have the most prolonged recumbent acid clearance times. The two major causes of this problem are impaired esophageal emptying and impaired salivary function. Abnormal acid clearance improves with an erect posture, suggesting that gravity compensates for impaired fluid emptying ***(Cook et al., 2012)..***

Esophageal emptying in GERD:

Two mechanisms of impaired esophageal emptying have been identified:

- Peristaltic dysfunction, resulting in either failed or hypotensive (<30 mmHg) peristaltic contractions. Peristaltic dysfunction becomes more common with increasing severity of esophagitis. Whether peristaltic dysfunction associated with peptic esophagitis is reversible is disputed. Most likely, acute dysfunction associated with active esophagitis is partially reversible, while chronic dysfunction associated with stricturing or extensive fibrosis is not. ***(Clarke et al., 2008)***.