The Utility of Narrow Band Imaging in Improving the Endoscopic Diagnosis of Gastroesophageal Reflux Disease

KWONG–MING FOCK, ENG–KIONG TEO, TIING–LEONG ANG, JESSICA YI–LYN TAN, and NGAI–MOH LAW

Division of Gastroenterology, Department of Medicine, Changi General Hospital, Singapore

Background & Aims: Narrow band imaging (NBI) facilitates mucosal surface evaluation and may improve the endoscopic diagnosis of gastroesophageal reflux disease (GERD). We investigated the utility of NBI in improving the endoscopic diagnosis of GERD when compared with conventional endoscopy. Methods: A total of 107 subjects (nonerosive reflux disease [NERD], 36; erosive reflux disease [ERD], 41; controls, 30) were recruited prospectively. The mucosal morphology at the squamocolumnar junction (SCJ) in GERD and controls was visualized using conventional endoscopy and NBI. The main outcome measurements were as follows: (1) The differences in mucosal morphology at the SCJ between conventional endoscopy and NBI; and (2) the differences in mucosal morphology at the SCJ between GERD and controls with NBI. Results: Micro-erosions, increased vascularity, and pit patterns at the SCJ not seen on conventional endoscopy were well seen with NBI. Compared with controls, ERD and NERD had a significantly higher prevalence of micro-erosions (ERD, 100%; NERD, 52.8%; controls, 23.3%), and increased vascularity (ERD, 95.1%; NERD, 91.7%; controls, 36.7%), but a lower prevalence of round pit pattern (ERD, 4.9%; NERD, 5.6%; controls, 70%). ERD and NERD were similar in terms of increased vascularity and pit patterns. Increased vascularity with absence of round pit pattern was useful to distinguish NERD from controls (sensitivity, 86.1%; specificity, 83.3%). Interobserver agreement was good for increased vascularity ($\kappa = 0.95$) and micro-erosions ($\kappa = 0.89$), but lower for pit pattern ($\kappa = 0.59$). Conclusions: NBI enhanced mucosal morphology at the SCJ and appeared useful for improving the endoscopic diagnosis of GERD.

Gastroesophageal reflux disease (GERD) is common in the Western population\(^1\) and recent studies have shown an increased prevalence of GERD in Asia as well.\(^2\) The diagnosis of erosive reflux disease (ERD) is based on the endoscopic detection of mucosal breaks at the squamocolumnar junction (SCJ). Nonerosive reflux disease (NERD) is characterized by reflux symptoms with no mucosal breaks seen at conventional endoscopy. In Asia, a greater proportion of patients have NERD compared with the West. Barrett’s esophagus (BE) also is uncommon in Asia, in contrast to the West.\(^3,4\) In the diagnosis of BE, it may be difficult to detect the short-segment form, especially when the length is less than 1 cm. Biopsies from short segments or tongues of columnar mucosa reveal specialized intestinal metaplasia in only 40% to 60% of patients.\(^5\) There is a need for better techniques of visualizing the SCJ to improve endoscopic diagnosis in GERD.

Magnifying chromoendoscopy has been used in the evaluation of GERD and BE. GERD has been associated with increased vascularity at the SCJ\(^6,7\) and Sharma et al\(^16\) assessed the utility of NBI in patients with GERD symptoms and found that compared with controls, a significantly higher proportion of patients with GERD had increased number, dilatation, and tortuosity of intrapapillary capillary loops (IPCLs), presence of micro-erosions, and increased vascularity at the SCJ. This suggested that NBI may represent an improvement over standard endoscopy for the diagnosis of GERD. Nonetheless, these are preliminary data and further corroborative studies are needed to determine whether NBI really improved the endoscopic diagnosis of GERD.

This prospective study investigated the utility of NBI in improving the endoscopic diagnosis of GERD. It evaluated the differences in mucosal morphology at the SCJ between conventional endoscopy and NBI in GERD and asymptomatic controls. Unlike the existent GERD-related NBI studies by Lee et al\(^13\) and Sharma et al,\(^16\) we used the more widely available Olympus Evis Exera II NBI video imaging system (Olympus

Abbreviations used in this paper: BE, Barrett’s esophagus; ERD, erosive reflux disease; GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; IPCL, intrapapillary capillary loop; NBI, narrow band imaging; NERD, nonerosive reflux disease; PPI, proton pump inhibitor; SCJ, squamocolumnar junction.
Optical, Tokyo, Japan), which used digital, rather than optical, magnification.

Materials and Methods

Overview of Study Design

In this prospective study conventional endoscopy and NBI were used to investigate the differences in mucosal morphology at the SCJ between GERD patients and asymptomatic controls. It was conducted during the period from July 2005 to July 2006, according to the principles of good clinical practice and the revised Declaration of Helsinki. The study protocol was approved by the hospital institutional review board. Informed consent was obtained from all patients before endoscopy.

Study Population

Inclusion criteria. Consecutive patients with symptomatic GERD, as defined by a GERD health-related quality-of-life (HRQL) heartburn score of more than 10, were recruited. These GERD patients had been referred for endoscopy and were not on long-term proton pump inhibitors (PPIs). Asymptomatic volunteers with no prior history of GERD and a GERD-HRQL score of 0 were recruited as controls.

Exclusion criteria. Patients who had undergone previous upper-gastrointestinal surgery such as gastrectomy, fundoplication, or distal esophagectomy, as well as those who were on continuous treatment with acid suppression in the preceding 4 weeks before endoscopy, and patients with BE, were excluded from the study. Patients with heartburn but no response to PPI and normal pH studies also were excluded.

Pilot Study

Before commencing the study, consecutive patients with GERD and asymptomatic controls were evaluated by the 3 experienced endoscopists (K.-M.F., E.-K.T., and T.-L.A.) performing the study to standardize the interpretation of endoscopic findings using conventional and NBI endoscopy. Based on these initial evaluations, the definitions of the endoscopic findings were agreed upon.

Definitions

Endoscopic findings. Mucosal breaks were defined as areas of slough or erythema clearly demarcated from adjacent normal-appearing mucosa. Micro-erosions were defined mucosal breaks not visible on standard endoscopy but present with NBI. Increased vascularity at the SCJ was defined as vascular spots or punctate erythema above the SCJ16 and/or increased erythema just below the SCJ. Based on concomitant evaluation using the Olympus Evis Lucea system that had NBI with optical magnification, which allowed us to characterize the morphology of these punctate spots above the SCJ during the pilot phase, we confirmed that these lesions corresponded to the IPCLs described by Sharma et al.16 However, because we used the Olympus Evis Exera II video imaging system, which used digital magnification for NBI for our study, we could not characterize the individual morphology of IPCLs that were seen as punctate dots. Mucosal pit patterns at the SCJ were defined as round, straight, long oval, tubular, and villous. A mucosal island was defined as an island of columnar epithelium above the SCJ.

Case definitions. The diagnosis of ERD was based on the Los Angeles Classification. NERD was defined based on the presence of reflux symptoms with a GERD-HRQL score of more than 10, the absence of mucosal breaks at conventional endoscopy, and a treatment response to PPI. NERD patients not responding to PPI underwent pH studies that, if normal, would lead to classification as functional heartburn and exclusion from further analysis. True controls were asymptomatic healthy volunteers without a prior history of GERD, a GERD-HRQL score of 0, and no mucosal breaks on conventional endoscopy. If micro-erosions were detected during NBI, controls were invited to undergo pH studies to exclude asymptomatic GERD.

Equipment and Endoscopic Procedure

The endoscopic procedures for all patients were performed using the same video gastroscope (XGIF-H160Y2; Olympus), video processor (CV-160B; Olympus), lighting unit (CLV-160B; Olympus), and high-definition liquid crystal display (LCD) monitor (OEV-191H; Olympus) by 3 experienced endoscopists (K.-M.F., E.-K.T., and T.-L.A.). The endoscopist was blinded to the GERD-HRQL score of the subjects.

Endoscopy was performed under conscious sedation using either intravenous midazolam or combined with intravenous fentanyl. Conventional endoscopy was first performed. A complete evaluation of the stomach and duodenum was performed, and biopsy specimens were taken for a rapid urease test to assess for Helicobacter pylori infection. Next, the cardia, SCJ, and distal esophagus were examined. The presence of hiatal hernia, ERD, and columnar-lined esophagus were noted. The SCJ was reexamined using NBI under normal as well as digital magnification of 1.5×. Micro-erosions and increased vascularity (prominent IPCLs above the SCJ, and vascular congestion below the SCJ), as well as the mucosal pit pattern below the SCJ, and the presence of columnar islands in the distal esophagus were recorded. Representative conventional and NBI images were recorded digitally. When BE was suspected, targeted biopsy specimens were obtained to look for specialized intestinal metaplasia.

Statistical Analysis

The main outcome measurements were the differences in mucosal morphology at the SCJ between conventional endoscopy and NBI, and the differences in mucosal morphology at the SCJ between GERD and controls with NBI. Two-sample t tests were used to compare the mean values of continuous variables, and the chi-square test was used to analyze categoric variables. Statistical tests were 2-sided and were performed using SPSS version 9.0 (SPSS Inc, Chicago, IL). A P value of less than .05 was statistically significant. To evaluate interobserver variability in the assessment of micro-erosions, increased vascularity, and mucosal pit patterns on NBI, the endoscopic digital images were reviewed independently by the 3 endoscopists who performed the procedures. The kappa statistic, a measure of agreement over and above chance, was analyzed by using the statistical software StatsDirect version 2.6.2 (StatsDirect, Cheshire, UK). The strength of agreement was defined as follows: kappa less than 0.2, poor; greater than 0.2 to 0.4 or less,
fair; greater than 0.4 to 0.6 or less, moderate; greater than 0.6 to 0.8 or less, good; greater than 0.8 to 1 or less, very good.

Results

Patient Demographics

A total of 107 subjects met the study criteria (GERD, 77; controls, 30) and were recruited. GERD patients were significantly older than controls (45.1 vs 39.0 y). Compared to controls, a higher proportion at GERD patients were male (50.6% vs 20.0%) and had hiatus hernia (54.5% vs 23.3%). The prevalence of H pylori was similar between the 2 groups (Table 1).

Results of Conventional Endoscopy

Among the 77 symptomatic GERD patients, 36 cases were diagnosed as NERD based on the presence of symptoms, normal conventional endoscopy (Figure 1), and response to PPI. In addition, there were 41 cases of ERD (LA grade A, 32; LA grade B, 9). All the 30 controls included in the study had normal conventional endoscopy.

Results of Narrow Band Imaging

NBI improved the visualization of the SCJ compared with conventional endoscopy (Table 2). The presence of micro-erosions at the SCJ, increased vascularity (Figure 2), and type of mucosal pit pattern (Figures 3, 4, and 5) below the SCJ not seen on conventional endoscopy were well seen on NBI. The mucosal islands in the distal esophagus were better visualized with NBI. There was a significant association of micro-erosions with the presence of increased vascularity at the SCJ for GERD patients compared with controls (overall, 89.6%; ERD, 95.1%; NERD, 100%; controls, 28.6%; P < .001). This difference between GERD and controls persisted even after adjusting for age and sex in the statistical analysis.

Narrow band imaging differences between erosive reflux disease and asymptomatic controls. Mucosal breaks and micro-erosions were seen in all ERD patients (100%) compared with 23.3% of asymptomatic controls who had micro-erosions with NBI (P < .001). Increased vascularity at the SCJ was present in 95.1% of patients with ERD, compared with 36.7% in controls (P < .001). There was a significant difference in pit-pattern distribution between ERD patients and controls. For ERD patients, a tubular pattern was present in 56.1%, a villous pattern in 22.0%, a straight pattern in 17.1%, and a round pattern in 4.9%, compared with 70% round, 20% straight, and 10% tubular patterns in controls (P < .001).

Narrow band imaging differences between nonerosive reflux disease and asymptomatic controls. Among the NERD patients, NBI revealed the presence of micro-erosions in 52.8% versus 23.3% in controls (P < .001) and increased vascularity at the SCJ in 91.7%, compared with 36.7% in controls (P < .001) (Table 3). In terms of pit-pattern distribution, in NERD patients 5.6% were round, 19.4% were straight, 52.8% were tubular, and 22.2% were villous, compared with 70%

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Table 1. Clinical Characteristics of GERD Patients Versus Controls

<table>
<thead>
<tr>
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<th>GERD (N = 77)</th>
<th>Controls (N = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>45.1</td>
<td>39.0</td>
<td>.041</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>39:38</td>
<td>6:24</td>
<td>.004</td>
</tr>
<tr>
<td>Presence of hiatus hernia</td>
<td>55.8%</td>
<td>23.3%</td>
<td>.004</td>
</tr>
<tr>
<td>H pylori present</td>
<td>27.3%</td>
<td>20.0%</td>
<td>NS</td>
</tr>
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</table>

Table 2. NERD: Conventional Versus NBI Endoscopy

<table>
<thead>
<tr>
<th></th>
<th>Conventional endoscopy</th>
<th>NBI endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-erosions</td>
<td>0%</td>
<td>52.8%</td>
</tr>
<tr>
<td>Increased vascularity at SCJ</td>
<td>0%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Mucosal islands</td>
<td>5.6%</td>
<td>38.9%</td>
</tr>
</tbody>
</table>

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Figure 1. A mucosal island at the SCJ detected using NBI.

Figure 2. NBI findings of dilated IPCLs at the distal esophagus.
round, 20% straight, and 10% tubular patterns in controls ($P < .001$). The combination of increased vascularity with absence of round pit pattern allowed NERD to be distinguished from controls with a sensitivity of 86.1% and a specificity of 83.3%. Positive and negative predictive values were 86.1% and 83.3%, respectively.

Narrow band imaging differences between erosive reflux disease and nonerosive reflux disease. ERD and NERD patients were similar in terms of increased vascularity at the SCJ and the type of pit patterns (Table 4). The only significant difference with NBI between ERD and NERD was the prevalence of mucosal breaks and/or micro-erosions (100% vs 52.8%).

Interobserver Variability

To determine interobserver variability in terms of recognition of mucosal micro-erosions, mucosal islands, presence of increased vascularity at the SCJ, and the type of pit patterns, the endoscopic digital images of 52 subjects were randomly chosen and reviewed. There was very good interobserver agreement for the presence of micro-erosions (kappa, 0.89; SE, 0.08; $P < .0001$) and increased vascularity at the SCJ (kappa, 0.95; SE, 0.08; $P < .0001$) on NBI. Overall, the interobserver agreement was moderate for the type of mucosal pit pattern (kappa, 0.59; SE, 0.05; $P > .0001$). Subanalyzed based on the type of pit pattern, the agreement was very good for villous pit pattern (kappa, 0.82) and round pit pattern (kappa, 0.80), but only moderate for tubular pit pattern (kappa, 0.53) and fair for straight and long oval pit patterns (kappa, 0.23 and 0.37, respectively).

Discussion

Our study showed that NBI improved the visualization of the SCJ by enhancing the contrast between the esophageal mucosa and gastric mucosa such that mucosal breaks and micro-erosions could be seen more easily and clearly with NBI than with standard endoscopy. It was able to detect the presence of increased vascularity at the SCJ and micro-erosions not seen on conventional endoscopy. NBI findings of micro-erosions, increased vascularity at the SCJ, and mucosal pit pattern other than round pit pattern were associated with the diagnosis of GERD. Although the interobserver agreement was lower for the specific types of mucosal pit pattern, it was not crucial because GERD was associated with nonround pit patterns and round pit patterns could be identified consistently. NBI was useful in distinguishing NERD from normal controls. NBI revealed the presence of increased vascularity in 91.7% of NERD patients, compared with 36.7% in controls. ERD and NERD patients were similar in terms of the prevalence of increased vascularity, suggesting that these NBI findings are common to patients with GERD. Although theoretically the increased vascularity could arise as a consequence of carditis owing to $H$ pylori infection, this was unlikely because the prevalence of $H$ pylori infection was similar between GERD patients and controls. The combination of increased vascularity with the

### Table 3. NBI: NERD Patients Versus Controls

<table>
<thead>
<tr>
<th>NBI findings</th>
<th>NERD (n = 36)</th>
<th>Controls (n = 30)</th>
<th>$P$</th>
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</thead>
<tbody>
<tr>
<td>Micro-erosions</td>
<td>52.8%</td>
<td>23.3%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Increased vascularity at SCJ</td>
<td>91.7%</td>
<td>36.7%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mucosal islands</td>
<td>38.9%</td>
<td>50%</td>
<td>NS</td>
</tr>
<tr>
<td>Proportion of round pit pattern</td>
<td>5.6%</td>
<td>70%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Table 4. NBI: NERD Patients Versus ERD Patients

<table>
<thead>
<tr>
<th>NBI findings</th>
<th>NERD (n = 36)</th>
<th>ERD (n = 41)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased vascularity at SCJ</td>
<td>91.7%</td>
<td>95.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Mucosal islands</td>
<td>38.9%</td>
<td>58.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Proportion of round pit pattern</td>
<td>5.6%</td>
<td>4.9%</td>
<td>NS</td>
</tr>
</tbody>
</table>
absence of a round pit pattern differentiated NERD from controls with a sensitivity of 86.1% and a specificity of 83.3%. The presence of mucosal islands was not useful in differentiating NERD patients from controls. This is not surprising because it is recognized that these islands may simply be ectopic gastric mucosa or pancreatic metaplasia, rather than GERD-related.

Our results are consistent with 2 recent publications concerning the use of NBI in GERD. Lee et al. showed that by improving the contrast between esophageal mucosa and gastric mucosa there was improved consistency in the grading of ERD. Sharma et al. showed that increased vascularity at the SCJ and increased, tortuous, and dilated IPCLs and micro-erosions all were associated with GERD. Unlike these 2 studies that used a prototype based on the Evis Lucera system, which came with digital magnification, our results were derived from NBI using the Olympus Evis Exera II video imaging system, which used optical magnification. Hence, we were not able to comment specifically on the morphology of dilated or abnormal IPCLs. Nonetheless, the diagnostic criteria that we used for NERD (ie, ca(ierdinal symptoms and response to PPI) are well-accepted criteria. Although the LA classification was based on conventional endoscopy, micro-erosions seen only on NBI actually may represent mucosal injury caused by GERD, reflecting ERD that had not been detected using conventional endoscopy. In the study by Sharma et al., micro-erosions were visualized in 30% of NERD patients. On the other hand, in the study by Sharma et al., none of the controls had micro-erosions, whereas in our study 23% of controls had micro-erosions. The presence of micro-erosions in the 7 controls may represent either asymptomatic GERD or asymptomatic pH study-negative volunteers. The possibility of asymptomatic ERD has been documented by other investigators. In fact, a population-based endoscopy study from Sweden showed that 36.8% of patients with ERD were actually completely asymptomatic on questionnaire, and the absence of symptoms could not be attributed to the use of acid suppressants. We performed pH studies in 4 of the controls with micro-erosions and these pH studies were negative. The negative pH studies showed that micro-erosions also could arise in asymptomatic, pH study-negative volunteers. An impedance study would have been useful to assess whether nonacid reflux was present in these cases, but this was not part of the present study design.

Finally, we used the Olympus Evis Exera II rather than the Evis Lucera video imaging system and therefore could perform only single-center study, and further corroborative works are needed to confirm these data. Further multiple prospective studies are needed to improve the detection of ERD.

We acknowledge the limitations of our study. First, this was a single-center study, and further corroborative works are necessary. There were differences in age and sex distribution between cases and controls, raising the possibility of confounding factors. Cases and controls were not matched perfectly because we enrolled consecutive subjects who gave informed consent. Nonetheless, when we adjusted for age and sex in our statistical analysis, the differences between GERD and controls remained, suggesting that age and sex were not confounding factors. We acknowledge that there could be selection bias in our study population because not all NERD patients and controls underwent pH studies. Nonetheless, the diagnostic criteria that we used for NERD (ie, ca(ierdinal symptoms and response to PPI) are well-accepted criteria. Although the LA classification was based on conventional endoscopy, micro-erosions seen only on NBI actually may represent mucosal injury caused by GERD, reflecting ERD that had not been detected using conventional endoscopy. In the study by Sharma et al., micro-erosions were visualized in 30% of NERD patients. On the other hand, in the study by Sharma et al., none of the controls had micro-erosions, whereas in our study 23% of controls had micro-erosions. The presence of micro-erosions in the 7 controls may represent either asymptomatic GERD or asymptomatic pH study-negative volunteers. The possibility of asymptomatic ERD has been documented by other investigators. In fact, a population-based endoscopy study from Sweden showed that 36.8% of patients with ERD were actually completely asymptomatic on questionnaire, and the absence of symptoms could not be attributed to the use of acid suppressants. We performed pH studies in 4 of the controls with micro-erosions and these pH studies were negative. The negative pH studies showed that micro-erosions also could arise in asymptomatic, pH study-negative volunteers. An impedance study would have been useful to assess whether nonacid reflux was present in these cases, but this was not part of the present study design. Finally, we used the Olympus Evis Exera II rather than the Evis Lucera video imaging system and therefore could perform only single-center study, and further corroborative works are needed to confirm these data. Further multiple prospective studies are needed to improve the detection of ERD.
define the role of NBI, especially with regard to the issues of interobserver agreement and the reproducibility of results.

References


Address requests for reprints to: Professor Kwong-Ming Fock, Division of Gastroenterology, Department of Medicine, Changi General Hospital, 2 Simel Street 3, Singapore 529889. e-mail: kwong_ming_fock@cgh.com.sg; fax: (65) 67816202.

The authors disclose no conflicts.