Diseases of the Esophagus (2001) **14,** 235–238

DISEASES OF THE ESOPHAGUS

Original article

Gastro-esophageal reflux disease confined to the sphincter*

J. Theisen,[1] S. Öberg,[2] J. H. Peters,[3] O. Gastal,[3] C. G. Bremner,[3] R. Mason,[3] T. R. DeMeester[3]

[1]*Department of Surgery, Technische Universitaet Muenchen, Munich, Germany;* [2]*Department of Surgery, Lund University, Lund, Sweden;* [3]*Department of Surgery, USC Keck School of Medicine, Los Angeles, CA, USA*

SUMMARY. **It has been shown previously that patients with gastro-esophageal reflux disease (GERD) do not always have increased esophageal acid exposure on 24 h pH monitoring. The recent recognition of carditis as a sensitive marker for GERD raises the possibility for patients with mild disease to have normal esophageal acid exposure but inflamed cardiac mucosa on biopsies of the cardia, which may be an early sign of GERD. To test this hypothesis, 171 consecutive patients evaluated for symptoms of GERD and no increased esophageal acid exposure, Barrett's esophagus or erosive esophagitis were divided into those with and without carditis. Esophageal acid exposure and lower esophageal sphincter (LES) characteristics were compared between the two groups. Comparisons were done using the Mann–Whitney *U*-test for non-parametric data. There were 82 patients with histologic evidence of carditis and 89 patients without carditis. Patients with carditis had a more deteriorated sphincter, determined by overall and abdominal length and resting pressure, and significantly higher esophageal acid exposure ($P < 0.05$). Patients with symptoms of GERD and histologic evidence of carditis may have early or mild reflux disease, which is confined to the sphincter.**

INTRODUCTION

Over the last decade the complications of chronic gastro-esophageal reflux disease (GERD), such as Barrett's esophagus and esophageal adenocarcinoma, have become a major health concern. It is estimated that about 2.6 million Americans are likely to develop Barrett's esophagus.[1] Once present, Barrett's epithelium is at risk of developing adenocarcinoma of the esophagus.[2,3]

To date, the severity of GERD has been objectively assessed using histologic proven injury to the esophagus and a 24-h pH probe placed 5 cm above the upper border of the lower esophageal sphincter (LES). However, several studies have shown that not all patients with symptoms suggestive of GERD, such as heartburn and regurgitation, have increased esophageal acid exposure or known histologic evidence of inflammatory changes.[4–6] The recent recognition of inflamed cardiac-type mucosa at the gastro-esophageal junction gave rise to a new concept of the progression of GERD.[7,8] The gastro-esophageal junction may be susceptible to the injurious effects of duodeno-gastric reflux leading to an inflamed cardiac-type mucosa. With deterioration of the sphincter, the refluxate then has access to the esophagus and may lead into a columnar-lined epithelium such as Barrett's mucosa. We have previously shown that cardiac mucosa, when present, is almost always inflamed, that it is associated with the hallmarks of reflux disease, and we suggested that cardiac-type mucosa is not a normal finding.[7] In the present study we hypothesize that GERD in the early stages may be limited to the gastro-esophageal junction and may identified by the presence of inflamed cardiac-type mucosa.

MATERIALS AND METHODS

Study population

The study population consisted of 171 consecutive patients with symptoms suggestive of GERD, normal esophageal acid exposure on 24 h pH monitoring, and no endoscopic esophageal mucosal injury. There were 110 women and 61 men with a median age of 50 years, range 18–89 years. Symptoms consisted of heartburn, regurgitation, dysphagia, non-cardiac chest pain,

Address correspondence to: Dr J. Theisen, Department of Surgery, Technische Universitaet Muenchen, Ismaningerstr.22, 81675 Munich, Germany. Tel: (+49) 894 1402115; Fax: (+49) 894 1404940; E-mail: theisen@nt1.chir.med.tu-muenchen.de
*This paper was presented at the ISDE meeting, Montreal, September 1998.

epigastric pain, or pain suggestive of aspiration such as recurrent pneumonia, wheezing or persistent cough. Patients with named motility disorders or a history of previous gastric or esophageal surgery were excluded from the study. All patients underwent upper endoscopy with biopsy, stationary manometry, and 24 h pH monitoring. Ninety-one patients underwent additional 24-h bilirubin monitoring in the esophagus.

Endoscopy

A standardized protocol for performing the upper endoscopy was applied to all the patients. The gastro-esophageal junction was identified by the proximal extent of the gastric rugal folds and multiple biopsies were taken. A change from pink-appearing glandular mucosa to the white pearly appearing squamous mucosa was considered to be the squamo-columnar junction. In patients with an irregular squamo-columnar junction which coincided with the gastro-esophageal junction, biopsies were taken from the tongues of glandular mucosa extending into the esophagus. Patients with a hernia had biopsies obtained from four quadrants at 2 cm intervals throughout the length of the separation of the squamo-columnar junction from the gastro-esophageal junction.

Histology

All biopsies were hematoxylin and eosin stained and analyzed for the type and condition of the epithelium. Cardiac type or columnar mucosa was characterized by a columnar epithelium with glands entirely composed of mucous cells without any parietal or chief cells. Inflammation of this mucosa was diagnosed in the presence of eosinophil or plasma cell infiltration of the lamina propria and hyperplasia of the mucous cells in the foveolar region. Specialized intestinal metaplasia was defined by the presence of well-defined goblet cells on routine sections and confirmed by positive staining with Alcian blue at pH 2.5. Additionally, the presence of *Helicobacter pylori* infection was assessed in all biopsy specimens.

Stationary manometry

The study was performed after an overnight fast. A water-perfused motility catheter was used. Lower esophageal sphincter characteristics were assessed as previously described. The parameters used to determine the integrity of the sphincter were calculated from the mean of five measurements. A defective LES was defined by the presence of one or more of the following criteria: a resting pressure < 6 mmHg, an overall length of < 2 cm, and/or an abdominal length of < 1 cm.

Ambulatory 24-h pH and bilirubin monitoring

Esophageal pH monitoring was performed using a glass electrode (Ingold Inc., Urdorf, Switzerland) and placed 5 cm above the manometrically defined upper border of the LES. The patients were asked to stop taking their antacid medications at least 72 h prior to the test, except for omeprazole which was discontinued at least 2 weeks earlier. The pH was recorded on a portable digital recorder and was analyzed as previously described. Patients with an esophageal pH < 4 for more than 4.4% of the recording time were considered as having increased esophageal acid exposure. Bilirubin exposure was measured simultaneously in the same position with a fiberoptic probe (Bilitec 2000, Synectics Inc., Stockholm, Sweden) as described elsewhere. A fraction time of $> 2.2\%$ above an absorption threshold of 0.2 was considered to show increased esophageal bilirubin exposure.

Study groups

The study population was divided into two groups. One group consisted of the patients in whom inflamed cardiac-type mucosa was found on biopsy and the comparison group consisted of patients without inflamed cardiac-type mucosa. There were 89 patients with carditis and 82 patients without carditis.

Statistic analysis

Data are reported as medians and interquartile ranges (IQR). To compare proportions, chi-squared analysis and Fischer's exact test were used. Comparison between individual groups was performed using Mann–Whitney *U*-test for non-parametric data.

RESULTS

There were no significant differences in the demographics between the two groups. The median age was 49 years (range, 23–76) and 51 (range, 18–89), respectively. There was a 2:1 female/male ratio in both groups.

Table 1 shows the prevalence of hiatal hernias within the two groups, demonstrating a significantly higher prevalence of hiatal hernias in patients with carditis ($P = 0.007$).

Table 1. Prevalence of hiatal hernia (Fischer's exact test)

	Carditis	No carditis	Total	*P*-value
No hernia	57	68	125	NS
Hernia	32	14	46	0.007
Total	89	82	171	

NS, not significant.

Table 2. Lower esophageal sphincter characteristics and 24-h pH monitoring in median and interquartile ranges

	Carditis ($n = 89$)	No carditis ($n = 82$)	P-value
Overall length (cm)	2.6 (1.8–3.2)	3.0 (2.2–3.5)	0.017
Abdominal length (cm)	1.2 (0.7–1.8)	1.6 (1.2–2.0)	0.017
Resting pressure (mmHg)	11.2 (5.5–16.4)	12.6 (8.4–20.2)	0.009
Total time pH < 4 (%)	1.2 (0.4–3.0)	0.6 (0.1–2.3)	0.007

The presence of *H. pylori* showed an inverse relationship of carditis vs. non-carditis. In the 91 patients undergoing additional Bilitec studies, there was no significant difference between the two groups.

Specialized intestinal metaplasia was found in eight patients. All were in the carditis group, giving a highly significant difference compared with the patients without carditis (P-value 0.007).

Considering that the study population selected for patients with normal 24 h pH studies, there was a statistically significant difference between the two groups for the overall percent time pH < 4, with a median of 0.6% (IQR: 0.1–2.3) for those patients in whom no carditis was diagnosed compared with a median of 1.2 (IQR: 0.4–3.0) in the carditis group (Table 2).

This was also true for the LES characteristics, which showed a more deteriorated sphincter in the group of patients with carditis, although still within the normal limits. There was a median pressure of 11.2 mmHg (IQR: 5.5–16.4) in the carditis group compared with a median pressure of 14.1 mmHg (IQR: 8.4–20.2) in the other group. The overall and abdominal length of the sphincter was significantly shorter in the carditis group (Table 2).

DISCUSSION

Our study suggests that inflamed cardiac-type mucosa may be a sign of early or mild reflux disease in as much as it consists of a group of patients who suffer from symptoms suggestive of GERD, who have a higher esophageal acid exposure (although within normal limits), and who demonstrate features of a more deteriorated LES compared with a group of patients in whom no inflamed cardiac-type mucosa was found. This suggests that, in the early stages of GERD, the disease may be limited to the sphincter and may be identified by the presence of carditis. This observation leads to a new definition of GERD. To date, GERD has been defined either by a positive 24-h pH study or by histologic evidence of inflammation within the esophagus. Normality has been defined either subjectively by the absence of symptoms or objectively by criteria assessed within the esophagus. The presence of carditis may identify a subgroup of patients with otherwise negative objective signs of reflux disease who nevertheless suffer from symptoms of GERD. Assuming that carditis may be the first step in the progression of reflux disease, medical or surgical treatment in this subgroup may prevent further progression. To clarify whether GERD develops as a multistep process initiated by inflamed cardiac-type mucosa, longitudinal studies with multiple endoscopies with biopsies are required. Reversibility of this mucosal damage by acid-suppression therapy or antireflux surgery could add additional information about the entity of this disease.

Hiatal hernia has been shown to be significantly linked to the severity of GERD.[9] We demonstrated a similar pattern by finding a higher prevalence of hiatal hernia in the group of patients with carditis. Therefore, we propose that, in the presence of symptoms suggestive of GERD and a hiatal hernia, the finding of inflamed cardiac mucosa on biopsy may identify those patients who have early reflux disease and may be in danger of developing 'traditional' GERD.

Assuming that carditis is an early sign of reflux disease, the inverse correlation of *H. pylori* and the presence of carditis conjuncts with published data about a possible protective effect of *H. pylori* for reflux disease.[10]

Further evidence for the theory that reflux of gastric contents is responsible for the presence of inflamed cardiac-type mucosa has recently been published by Katzka, Gideon and Castell.[11] In an elegant study they demonstrated a cardiac reflux pattern in normal volunteers by placing a 24-h pH probe 5 cm below the upper border of the LES. They concluded that the anatomic cardia may behave as a conduit for refluxed acid into the esophagus. Future studies have to correlate cardiac reflux pattern with the histologic diagnosis of inflamed cardiac-type mucosa.

In summary, we propose a new concept for the development of reflux disease. In a subgroup of patients, the gastro-esophageal junction may be susceptible to the injurious effects of gastric contents leading to an inflamed cardiac-type mucosa. This mucosal metaplastic change may be reversible with acid-suppression therapy or antireflux surgery. Slowly, deterioration of the lower esophageal sphincter in patients with medically uncontrolled reflux or inadequate antireflux procedures exposes the esophagus to the components of gastric juice, causing changes which are typical of esophageal reflux diseases such as Barrett's metaplasia.

References

1. Cameron A J. Epidemiologic studies and the development of Barrett's esophagus. Endoscopy 1993; 25: 635–636.
2. Cameron A J, Ott B J, Payne W S. The incidence of adenocarcinoma in columnar-lined (Barrett's esophagus). N Engl J Med 1985; 131: 857–859.

3. Hameeteman W, Tytgat G N J, Houthoff H J, Van den Theel J G. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterol 1989; 96: 1249–1256.
4. Csendes A, Smok G, Flores N, Rojas J, Quiroz J, Henriquez A. Comparison of clinical, endoscopic and functional findings in patients with intestinal metaplasia at the cardia, carditis and short-segment columnar epithelium of the distal esophagus with and without intestinal metaplasia. Dis Esoph 2000; 13: 61–68.
5. Spechler S J, Goyal R K. The columnar lined esophagus, intestinal metaplasia and Norman Barrett. Gastroenterol 1996; 110: 614–621.
6. Spechler S J, Zeroogian J M, Antonioli D A, Wang H H, Goyal R K. Prevalence of metaplasia at the gastro-esophageal junction. Lancet 1994; 344: 1533–1536.
7. Oberg S, Peters J H, DeMeester T R *et al*. Inflammation and specialized intestinal metaplasia of cardiac mucosa is a manifestation of gastro-esophageal reflux disease. Ann Surg 1997; 226: 522–532.
8. Clark G W, Ireland A P, Chandrasoma P, DeMeester T R. Inflammation and metaplasia in the transitional epithelium of the gastro-esophageal junction. A new marker for gastro-esophageal reflux disease. Gastroenterol 1994; 106: A63.
9. Stein H J, DeMeester T R. Complications of gastro-esophageal reflux disease. Role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure and duodenogastric reflux. Ann Surg 1992; 216: 35–43.
10. Oberg S, Peters J H, Nigro J J *et al*. Helicobacter pylori is not associated with the manifestations of gastro-esophageal reflux disease. Arch Surg 1999; 134: 722–726.
11. Katzka D A, Gideon R M, Castell D O. Normal pattern of acid exposure at the gastric cardia: a functional midpoint between the esophagus and stomach. Am J Gastroenterol 1998; 93: 1236–1242.