Digestive Diseases and Sciences, Vol. 50, No. 1 (January 2005), pp. 111–115 (© 2005)
DOI: 10.1007/s10620-005-1287-8

Gall Bladder Emptying in Patients with Corrosive-Induced Esophageal Strictures

BILAL A. KHAN, DM, RAKESH KOCHHAR, DM, BIRENDER NAGI, MD, KAISER RAJA, DM, and KARTAR SINGH, DM

Ingestion of corrosive substances can lead to strictures of the esophagus and stomach. Cicatrization of the lower part of the esophagus can entrap vagal fibers in the process of fibrosis. The aim of the present study was to evaluate gallbladder dysfunction as a sequel to vagal damage in patients with corrosive-induced esophageal strictures. The cephalic phase of gallbladder emptying was stimulated by modified sham feeding according to the chew-and-spit method. Gallbladder volume was measured by ultrasonography using the ellipsoid method after an overnight fast and every 15 min for a period of 90 min after sham feeding in 22 patients and 10 controls. Mean fasting gallbladder volume was significantly greater in patients than in controls (22.09 ± 9.78 vs. 14.61 ± 4.42 ml; $P = 0.025$). After sham feeding the gallbladder ejection fraction was significantly lower in patients than in controls (32.86 ± 17.21 vs. $49.40 \pm 7.86\%$; $P = 0.007$). Patients with cicatrization in the distal one-third of the esophagus had a greater basal gallbladder volume (24.57 ± 9.2 ml) and significantly lower ejection fraction ($20.47 \pm 8.9\%$) than patients with strictures at other sites (gallbladder volume, 18.50 ± 10.69 ml; ejection fraction, $47.48 \pm 13.3\%$; $P = 0.001$). In conclusion, patients with corrosive-induced esophageal strictures, especially those in the distal one-third, had an increased fasting gallbladder volume and decreased cephalic phase of gallbladder emptying, pointing to impaired vagal cholinergic transmission, possibly due to vagal entrapment in the cicatrization process.

KEY WORDS: gallbladder emptying; sham feeding; vagus; corrosive stricture; esophagus.

Ingestion of corrosive substances either accidentally or with suicidal intention is prevalent worldwide. Alkali ingestion is more common in the West, whereas acid ingestion is more common in India (1–3). Management of corrosive ingestion poses a serious clinical problem, as despite early treatment, morbidity remains high. Late complications of corrosive ingestion include esophageal stricture formation, gastric cicatrization, and esophageal carcinoma (1–4). The fibrotic sequelae of corrosive ingestion are linked to the severity of the injury, which can be assessed at the time of initial endoscopy. Zargar *et al*. (5) have reported that 71% of patients with grade IIb injury and all patients with grade III injury develop esophageal and/or gastric cicatrization.

Gallbladder contractions are regulated by different mechanisms during the interdigestive and digestive states (6, 7). During the interdigestive state, periodic fluctuations in motilin initiate contractions of the upper gastrointestinal tract, including the gallbladder (8). After feeding, the cephalic phase of gallbladder contraction is mediated through extrinsic nerves but most contractions are elicited through the action of cholecystokinin (CCK) released from the small bowel (9). CCK acts mostly through action on intrinsic cholinergic nerves, although a direct action on gallbladder muscle is possible.

The right and left vagus nerves form an esophageal plexus distributed over the surface of thoracic esophagus. Just above the esophageal hiatus the plexus forms

Manuscript received April 18, 2004; accepted July 27, 2004.
From the Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
Address for reprint requests: Dr. Bilal Ahmad Khan, Baitul Noor, New Zero Bridge, Raj Bagh, Srinagar J&K, India 190008; dr_bilalkhan@rediffmail.com.

anterior and posterior vagal trunks closely adherent to the esophageal wall (7). The gallbladder is innervated by the vagus via the hepatic branches of the anterior vagal trunk. We hypothesized that esophageal cicatrization following severe corrosive injury probably entraps vagal fibers surrounding the esophagus in the reparative process and this may lead to vagal dysfunction. We have shown earlier that patients with corrosive-induced esophageal strictures have impaired gastric emptying and hypochlorhydria, probably secondary to vagal dysfunction. The aim of the present study was to evaluate the cephalic phase of gallbladder emptying in patients with corrosive stricture of the esophagus.

MATERIALS AND METHODS

Between July 2000 and December 2001, 22 patients with symptomatic corrosive stricture of the esophagus and/or stomach attending the gastroenterology services of our hospital for endoscopic dilatation or surgery were recruited. Patients with gallstone disease, prior abdominal surgery, or history suggestive of autonomic neuropathy and those on medications known to interfere with gastrointestinal motility were excluded. The patient group consisted of 14 males and 8 females with a mean age of 32 ± 8.5 years (range, 16–55 years) and a mean body mass index (BMI) of 20 ± 3 kg/m^2. Ten healthy volunteers with a mean age of 33 ± 9.5 years (range, 19–52 years) and a mean BMI of 22 ± 2 kg/m^2 were taken as controls. All subjects gave informed consent and the study protocol was approved by the local ethics committee.

Patients were evaluated regarding the nature and duration of corrosive injury. Each patient was assessed clinically. Barium swallow and upper gastrointestinal endoscopy were carried out to define the site, length, and number of the esophageal stricture(s) and gastric involvement. After an overnight fast, gallbladder volume was measured by real-time ultrasonography (3.5-MHz RT 3600 transducer; Rancho, USA). Longitudinal and axial cross-sectional images of the gallbladder at its largest dimensions were obtained. The gallbladder volume was calculated using the ellipsoid method as described by Dodds *et al*. (10). Three measurements were obtained in rapid sequence and a mean value was used. Gallbladder emptying was studied in response to cephalic vagal stimulation induced by modified sham feeding (i.e., chew-and-spit method). At time 0 subjects were offered an appetizing meal (100 g cheese, 50 g wheat flour, potatoes, 125 g vegetables, 50 g soybean, and 15 g oil, providing 53 g protein, 45 g fat, and 58 g carbohydrate and a total of 825 calories) and allowed to smell, chew, and taste the items of preference for a 30-min period but not to swallow a single morsel of food. Gallbladder images were obtained every 15 min, from time 15 min to time 90 min. Gallbladder residual volume was the smallest volume at any time after the sham feed. The difference between the basal volume and the corresponding residual volume represented the gallbladder ejected volume (ml). The gallbladder ejection fraction (GBEF[%]) was calculated according to the formula, GBEF(%) = 1 − (residual volume/fasting volume) × 100.

Statistical Analysis. Results are expressed as mean ± SD. Comparison between patients and controls was performed by Student's t test. The level of significance was set at $P < 0.05$.

TABLE 1. GALLBLADDER MOTILITY IN PATIENTS WITH CORROSIVE STRICTURE AND CONTROLS

Gallbladder variable	*Patients with stricture* (n = *22*)	*Controls* (n = *10*)	P *value*
Fasting volume (ml)	22.09 ± 9.78	14.61 ± 4.42	0.025
Ejected volume (ml)	6.98 ± 4.73	7.40 ± 3.22	0.797
Residual volume (ml)	15.11 ± 7.72	7.21 ± 1.64	0.003
Ejection fraction (%)	32.86 ± 17.21	49.40 ± 7.86	0.007

RESULTS

Nineteen patients had ingested an acid (sulfuric acid, 11; hydrochloric acid, 5; nitric acid, 3), while the remaining 3 patients had ingested caustic soda. Thirteen patients had a single stricture, six patients had two strictures, and one patient had three strictures in the esophagus. The upper esophagus was involved in 12 (54.54%), middle esophagus in 10 (45.45%), and lower esophagus in 12 (54.54%) patients. The stomach was involved in seven (31.8%) patients, of whom two had no esophageal involvement.

Mean fasting gallbladder volume and residual volume were significantly greater in patients with corrosive intake than in controls ($P = 0.025$ and $P = 0.003$, respectively) (Table 1). The total amount of bile ejected did not differ significantly. After sham feeding the gallbladder ejection fraction (%) was significantly lower in patients (32.86 ± 17.21%) than in controls (49.40 ± 7.86%) ($P = 0.007$) (Figure 1).

Correlating gallbladder volume parameters with site of esophageal stricture showed that patients with lower esophageal involvement (EL) had greater fasting and residual gallbladder volumes than patients with involvement at other sites (non-EL) ($P = 0.18$ and 0.003, respectively) (Table 3). The volume and fraction of bile ejected after sham feeding were significantly lower in patients with lower esophageal cicatrization than in those with cicatrization at other sites in the esophagus ($P = 0.10$ and 0.0018, respectively) (Table 3 and Figure 2).

In patients with involvement of the stomach, fasting gallbladder volume and gallbladder emptying were not significantly different from those of controls (Table 2).

DISCUSSION

Ingestion of concentrated acids and alkalis can lead to varying degrees of injury to the gastrointestinal tract (1, 2). Patients with grade IIb or higher injury on endoscopy develop cicatrization, which can result in esophageal stricture formation and symptoms thereof (5). Gastric cicatrization becomes clinically significant if it produces outlet obstruction. Patients with esophageal stricture, particularly those involving the lower end, can have

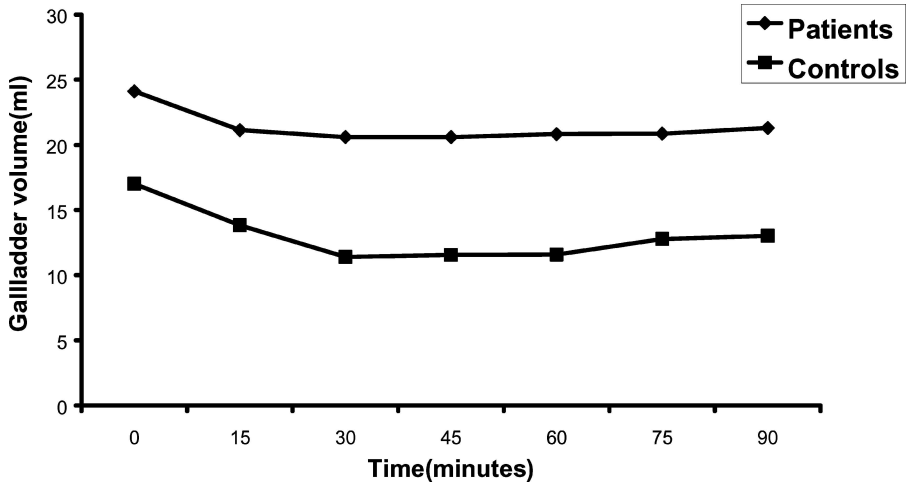

Fig 1. Gallbladder emptying curve in patients with corrosive stricture and controls.

entrapment of vagal nerve trunk fibers in the cicatrization process extending transmurally. Such patients could have vagal dysfunction as has been suggested in our previous work.

Our results show that gallbladder emptying in patients with corrosive-related sequelae involving the upper gastrointestinal tract is different from that in age- and sex-matched healthy controls. In patients with corrosive esophageal stricture, the mean fasting gallbladder volume was significantly increased. Several factors are known to influence fasting gallbladder volume. First, fasting gallbladder volume is related to body mass: a high BMI is correlated with an increased fasting gallbladder volume (11). However, the BMI in our patients with corrosive stricture was not significantly different from that in controls. Second, motilin plays a physiologic role in the regulation of gallbladder emptying in the fasted state (8, 9). CCK is involved in the regulation not only of postprandial gallbladder volume but also of fasting volume (12). Motilin and CCK levels and their effect on gall bladder tone need to be studied in these patients. Patients with stomach cicatrization had normal gallbladder motility, suggesting that motilin and CCK levels may not be altered by direct mucosal damage in these patients. Gallbladder tone is also regulated by vagal cholinergic input (13). After truncal vagotomy or during cholinergic blockade with atropine, gallbladder volume increases (14, 15). Therefore the increased fasting gallbladder volume might be ascribed to vagal dysfunction.

Gallbladder emptying response to modified sham feeding was significantly reduced in patients with corrosive ingestion compared to controls. Sham feeding is one of the methods used to stimulate the cephalic phase of digestive functions. In patients with an intact vagus nerve, sham feeding induces a decrease in gallbladder volume and this effect is mediated via cholinergic pathways (16). It is possible that the gallbladder response to sham feeding is the result of inadvertent swallowing of the test meal. However, the participants were trained to chew and spit the meal and this was done under strict supervision. All the corrosive ingestion patients were taken for endoscopic evaluation after modified sham feeding and no food particles were observed in the stomach. Duodenal acidification has also been discounted as a possible confounding factor in evaluation of gallbladder contraction after sham feeding (15). Moreover, our unpublished results suggest that corrosive ingestion patients have hypochlorhydria.

TABLE 2. GALLBLADDER MOTILITY IN PATIENTS WITH GASTRIC CICATRIZATION AND CONTROLS

Gallbladder variables	*Patients with cicatrization* (n = *7)*	*Controls* (n = *10)*	P *value*
Fasting volume (ml)	17.67 ± 8.27	14.61 ± 4.42	0.33
Ejected volume (ml)	6.24 ± 3.65	7.40 ± 3.22	0.49
Residual volume (ml)	11.43 ± 8.50	7.21 ± 1.64	0.14
Ejection fraction (%)	41.75 ± 22.85	49.40 ± 7.86	0.33

TABLE 3. GALLBLADDER MOTILITY IN PATIENTS WITH CORROSIVE-INDUCED LOWER ESOPHAGEAL CICATRIZATION (EL) AND CICATRIZATION AT OTHER SITES (NON-EL)

Gallbladder variables	*EL* (n = *12)*	*Non-EL* (n = *10)*	P *value*
Basal volume (ml)	24.57 ± 9.2	18.51 ± 10.09	0.18
Residual volume (ml)	19.32 ± 6.51	9.73 ± 5.09	0.003
Ejection volume (ml)	5.24 ± 3.72	8.78 ± 5.53	0.10
Ejection fraction (%)	20.47 ± 8.00	47.48 ± 13.3	0.001

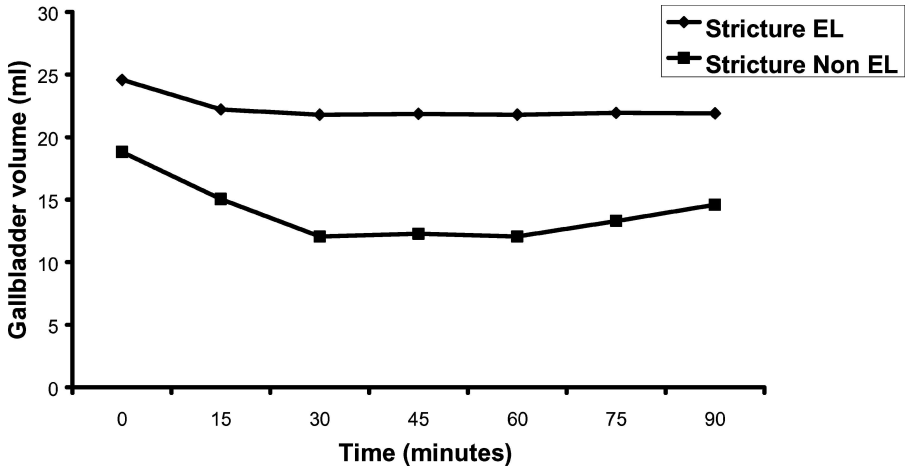

Fig 2. Gallbladder emptying curve in patients with stricture of the lower esophagus (EL) and stricture at other sites (non-EL).

Correlating gallbladder emptying response with modified sham feeding in relation to site of esophageal stricture showed that patients with esophageal cicatrization in the lower one-third had an increased fasting gallbladder volume and a significantly reduced ejection fraction compared to patients with stricture at other sites. This is in accordance with our previous work where patients with involvement of the distal one-third of the esophagus had significant hypochlorhydria and impaired gastric emptying.

Our results showing increased fasting gallbladder volumes and impaired gallbladder emptying in response to sham feeding suggest impaired vagal cholinergic transmission, probably due to entrapment of vagal fibers in the process of cicatrization of the distal esophagus in patients with severe injury due to corrosive ingestion. This phenomenon mimicks the effects of vagotomy. Masclee *et al*. (17) reported that patients with vagotomy had a greater mean gallbladder volume compared to controls. Fisher *et al*. (14) also reported that gallbladder volume increases after truncal vagotomy and modified sham feeding does not stimulate gallbladder emptying in these patients. Patankar *et al*. (15) also confirmed that vagotomized patients have a lower ejection fraction as compared to controls after meals.

Vagotomy leads to gallbladder hypotonia and impairs gallbladder emptying in the fasted state as well as in digestive state. Gallbladder stasis is a crucial element in gallstone formation. In addition, due to delayed intestinal transit secondary to vagal dysfunction, the circulating bile acid pool might increase, resulting in an increased biliary deoxycholic acid concentration, a risk factor for development of gallstones. Several clinical studies have documented an increase in the incidence of gallstones of four to six times after truncal vagotomy [18–20]. Although postprandial gallbladder emptying was not evaluated, these patients with corrosive esophageal strictures may be predisposed to gallstone disease.

In conclusion, gallbladder emptying is affected in patients with stricture of the distal esophagus, possibly related to vagal entrapment in the cicatrization process following severe corrosive injury. It is possible that these alterations predispose them to gallstone disease. Further studies are needed to evaluate postprandial gallbladder emptying in these patients.

REFERENCES

1. Zargar SA, Kochhar R, Nagi B, *et al*.: Ingestion of corrosive acids, spectrum of injury to the upper GI tract and natural history. Gastroenterology 97:702–707, 1989
2. Zargar SA, Kochhar R, Nagi B, *et al*.: Ingestion of strong corrosive alkalis, spectrum of injury to upper GI tract and natural history. Am J Gastroenterol 87:337–340, 1992
3. Goldman LP, Weigert JM: Corrosive substance ingestion. A review. Am J Gastroenterol 79:85–90, 1984
4. Dilawari JB, Singh S, Rao PN, *et al*.: Corrosive ingestion in man—A clinical endoscopic study. Gut 25:183–187, 1984
5. Zargar SA, Kochhar R, Mehta S, *et al*.: Role of fibre optic endoscopy in the management of burns. Gastrointest Endoc 37:165–169, 1991
6. Ryan JP: Motility of the gallbladder and biliary tree. *In* Physiology of the Gastrointestinal Tract. Johnson LP, Christensen J, Grossman MI, *et al*. (eds.). New York, 1986, p 473
7. Tierney S, Pitt HA, Lillemoe KD: Physiology and pathophysiology of the gallbladder motility. Surg Clin N Am 73:1267–1290, 1993
8. Luiking YC, Peeters TL, Stolk MFJ: Motilin induces gallbladder emptying and antral contraction in the fasted state in humans. Gut 42:830–835, 1998
9. Svenberg T, Christofides ND, Fitzpatrick ML, *et al*.: Interdigestive biliary output in man: relationship to fluctuations in plasma motilin and effect of atropine. Gut 23:1024–1229, 1982

10. Dodds WJ, Groh WJ, Darweesh RMA: Sonographic measurement of gallbladder volume. Am J Radiology 145:1009–1011, 1985
11. Masclee AA, Gielkens HA, Lieverse RJ: Gallbladder motility in response to sham feeding and cholecystokinin in lean and obese subjects. Digestion 58(1):43–49, 1997
12. Masclee AAM, Jansen JBMJ, Driessen WMM, *et al*.: Effect of truncal vagotomy on cholecystokinin release, gallbladder contraction and gallbladder sensitivity to cholecystokinin in humans. Gastroenterology 98:1338–1341, 1990
13. Wim PM Hopman, Jan BMJ Janson, Rosenbusch G: Cephalic stimulation of gallbladder contractions in humans: role of cholecystokinin and the cholinergic system. Digestion 38:197–203, 1987
14. Fisher R, Elizabeth R, Leon SM: Gallbladder emptying response to sham feeding in humans. Gastroenterology 90:1854–1857, 1986
15. Patankar R, Ozmen MM, Sanderson A: Effect of cisapride on gallbladder emptying and plasma CCK in normal and vagotomized human subjects. Dig Dis Sci 41:543–548, 1996
16. Robert SF, Elizabeth R, Leon SM: Cholinergic effects on gallbladder emptying in humans. Gastroenterology 89:716–722, 1985
17. Masclee AAM, Ledeboer ML, Giekens HG: Effect of erythromycin on gallbladder emptying in patients with antrectomy or truncal vagotomy. Am J Gastroenterology 90:973–977, 1995
18. Clave RA, Gaspar MA: Incidence of gallbladder disease after vagotomy. Am J Surg 118:169–173, 1969
19. Ihasz M, Griffith CA: Gallstone after vagotomy. Am J Surg 141:48–51, 1981
20. Friedmann GD, Kannel WB, Dawber TR: The epidemiology of gallbladder disease: observations of the Framingham study. J Chron Dis 19:273–281, 1966