

Causative Mechanism of Reflux Esophagitis induced by Digestive Secretions

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Mechanisms producing reflux esophagitis were experimentally evaluated to clarify a direct action of digestive secretions to the esophageal mucosa.

Mucosal lesions of reflux esophagitis were grossly composed of erosion, ulceration and loss of normal lustrous appearance. Based on histological examination, the degrees of erosion, ulceration and cell infiltration were also compared with respect to the severity of reflux esophagitis.

Causative mechanisms of reflux esophagitis due to gastric juice alone are different from those due to another digestive secretions in relation to either the gastrectomized status or not.

Key words: Gastric juice, intraluminal pH of the esophagus, esophageal ulcer

INTRODUCTION

It is well known that one of the formidable complications following total gastrectomy is reflux esophagitis as described by QUINKE¹⁾ in 1879. Much work has been detailed concerning its origin on the basis of pathophysiological aspects. As far as reflux esophagitis is concerned, experimental work is concentrated on an operative procedure of esophagogastrostomy.

The aim of this study is to clarify as to whether which of digestive secretions is mostly influential to produce reflux esophagitis, using an experimental model by which we experimentally designed to make the digestive secretions selectively regurgitated.

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METHOD AND MATERIAL

Adult Wister rats, 5 months of age, weighing 300g or more, were used. Rats were anesthetized with ether. Surgical procedures were designed for digestive secretions to regurgitate selectively to the esophagus.

Ninety rats were divided into the following experimental models, in which each group included 10 rats, as shown in Fig. 1, 1-A: after performance of total gastrectomy, the esophagus and jejunum were anastomosed end to end and the jejunum was ligated 15cm distal to the pyloric ring to make reflux of the pancreatic juice and bile. 1-B: The same as 1-A in addition to ligation of the common hepatic duct to produce reflux of the pancreatic juice. 1-C: The same as 1-A in addition to ligation of the pancreas adjacent to the common hepatic duct to bring reflux of the bile. 1-D: The same as 1-A in addition to ligation of both common hepatic duct and pancreas to

exclude reflux of the bile and pancreatic juice. 1-E: a 2cm incision on the esophagocardiac junction was made and subsequently closed with transverse suturing to impede the sphincter-like action of esophagocardiac junction. Then, the pyloric ring was tied to allow reflux of gastric juice alone. 1-F: The same as 1-E in addition to ligation placed on a 15cm jejunum distal to the pyloric ring to produce reflux of gastric and pancreatic juices, and the bile. 1-G: The same as 1-F in addition to ligation of the common hepatic duct to make reflux of gastric and pancreatic juices. 1-H: The same as 1-F in addition to ligation of the pancreatic duct to result in reflux of gastric juice and the bile. 1-I: The same as 1-F in addition to ligation of the common hepatic and pancreatic ducts. The intraluminal pH levels of the esophagus were measured with the use of pH-meter (E5-05 type Fuji Co.) prior to autopsy at the points of 1.5 cm (E_1) and 0.5 cm (E_2) away from the lower end of the esophagus. The pH-meter calibration was made with standard buffer solutions of pH7 and pH4.

At autopsy the esophagus was resected and longitudinally opened, fixed in 10% formalin, and sectioned and stained with hematoxylin and eosin.

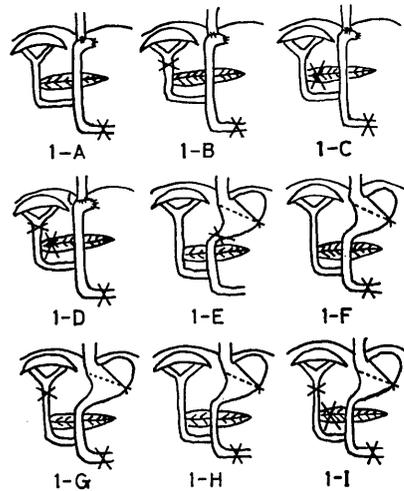


Fig. 1 Experimental shema divided into 9 groups, which are designed to enable digestive secretions of the gastric, pancreatic juice and the bile to regurgitate.

RESULTS

The pH levels were measured at two different sites (E₁ and E₂) among the 9 groups designed to selectively result in reflux of digestive secretions. In 1-A, 1-B, 1-C, 1-D and 1-G groups, the pH levels were high at both E₁ and E₂ in comparison with those prior to surgery as shown in Fig. 2. In 1-E group, the pH values were lowered, whereas in 1-F whereas slightly high at E₂. In 1-H group, there were slightly high at E₁ but variable at E₂. In 1-I group, these were almost constant at both E₁ and E₂. These results showed that the pH levels in the esophagus were influenced on reflux of gastric juice. When gastric juice failed to flow back to the esophagus, the pH levels declined to alkali and this tendency was significant in 1-D group. On gross appearance, the main mucosal changes of the esophagus comprised ulceration, loss of normal lustrous appearance as shown in Fig. 3.

In 1-A and 1-B groups without reflux of gastric juice, a few histologic changes in the mucosa of the esophagus were revealed. In either 1-E with reflux of gastric juice

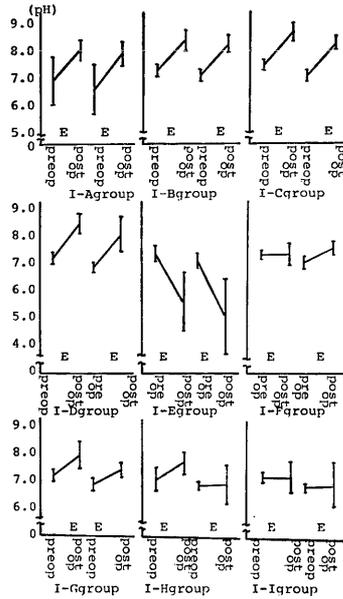


Fig. 2 Intraluminal pH values of the esophagus at the two different points of E₁ and E₂ among the 9 experimental groups. E₁: the point 0.5cm proximal to the esophagocardiac junction E₂: the point 1.5 cm proximal to the esophagocardiac junction.



Fig. 3 Ulcerative changes of the esophagus caused by reflux esophagitis on gross appearance.

alone or 1-F with reflux of a mixture of digestive sections, a varying variety of mucosal-changes was demonstrated as outlined in Table 1. The finding of mucosal thickness was not a predominant manifestation due to a short period of observation.

Main histologic findings in the mucosa of the esophagus were ulceration, cell infiltration, abscess formation, hyperkeratosis, and thin layer of the epithelium. The findings of erosion and ulceration were composed of either a defect of mucosal or submucosal layer. There were a few findings of abscess formation and hyperkeratosis, which was graded as slight, moderate (within less than 2 times the normal width of the epithelium) and severe (more than 2 times) as shown in Table 1. The term, thin layer of the epithelium, is an abnormal finding of demonstrating an ill defined margin between epithelial cells and narrowed basal cells. The lesions of ulceration and erosion were manifest in 1-E and 1-F as shown in Fig. 4 and scanty in 1-A, 1-B and 1-H. There was no significant

Table 1 Summary of histologic alterations of the wall of esophagus in the 9 groups.

group	I-A	I-B	I-C	I-D	I-E	I-F	I-G	I-H	I-I
No rate	10	10	10	10	10	10	10	10	10
macro erosion	2	2			10	10		4	
thickened ep									
loss of lustrous ep	10	10			10	10		8	
micro erosion	3	1			9	10		4	
cell infilt	6	6			10	10		5	1
abscess						3			
keratosis									
mild	9		10	10	10	10		10	6
moderate		10	3	4			10	3	6
severe									

ep: epithelium, macro: macroscopic finding
micro: microscopic finding



Fig. 4 Histologically ulcerative changes with slight degree of cell infiltration

difference between the degrees of cell infiltration. In 1-A and 1-B groups, histologic erosion and cell infiltration were not concomitantly seen whereas in 1-E, 1-F and 1-H groups these very often coexisted. The finding of hyperkeratosis was shown in all the specimens to some extent. It was moderate in 1-B, 1-C, 1-H, 1-I groups. The thin epithelial layer lesions were revealed in 1-B and 1-F groups.

DISCUSSION

With respect to reflux esophagitis, histological study has been reported by **QUINKE** in 1879. It is clear that pepsin and gastric free acid are mainly causative of reflux esophagitis. The analysis focused on postoperative reflux esophagitis following gastrectomy has been made since reported by **HERSINGEN**²⁾. Accidental complaints of reflux esophagitis are increasing in accordance with prevailing the indication for total gastrectomy and proximal gastrectomy of choice. In this study it is to clarify that which of digestive secretions regurgitated to the esophagus plays an important role in producing reflux esophagitis. The experimental models designed in rats enabled digestive secretions to flow backward to the esophagus selectively. In 1934, **SELYE**³⁾ reported the results of animal study as to reflux esophagitis. Since then, many reports⁴⁾⁻⁶⁾ have clarified mechanism and pathogenesis of reflux esophagitis. Most of them, however, are based on surgical destruction of the sphincter-like action in the cardia. Our study is specific of reflux esophagitis caused by individual digestive secretions.

SELYE³⁾ confirmed that ligation on the pyloric ring causes reflux esophagitis and **HELSINGEN** reported total gastrectomy tends to produce esophagitis lesions. In our study, ulcer formation on the mucosa of the esophagus occurred in 30% out of reflux of three digestive secretions of gastric and pancreatic juices, and bile and in 10% out of reflux of intestinal and pancreatic juices. There was nothing out of reflux of the bile. Ulcerative lesion was mostly significant in 1-F group. Reflux of either gastric juice or in combination with the bile plays an important role in developing ulceration related to reflux esophagitis. **GILLISON**⁷⁾ also noted that reflux of gastric juice combined with the bile predisposed the esophagus to reflux esophagitis. This findings were consistent with our results. Meanwhile, alterations of the pH levels were related to operative procedure of total gastrectomy. When the stomach was left intact, the pH levels in the esophagus did not change except for in 1-G group. It depends on neutralization by mixture of pancreatic juice or bile. Our results indicate that reflux esophagitis is not attributable to lowering pH level. Enzymic activity of pepsin and trypsin in gastric and pancreatic juices is an effective aid to its occurrence as reported by **REDO**⁸⁾. On the basis of this study, it is clear that gastric juice tends to bring erosion and ulceration to the esophageal mucosa. on the other hand, a mixture of bile, pancreatic and intestinal juices and/or pancreatic and intestinal juices are more likely to lead to cell infiltration and mucosal thickness without erosion and ulceration as histologic feature. Furthermore, it is suggestive that pepsin and trypsin exert on formation of reflux esophagitis in the proper pH conditions. A considerably

long duration of time is required for producing reflux esophagitis when pancreatic juice is mixed. It seems worthwhile to document that mechanisms of reflux esophagitis undergoing gastrectomy are different from that with the intact stomach.

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