Response of Lower Esophageal Sphincter Pressure to Beef Soup or AOC-Tetrapeptide Stimulation in Esophagitis

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NAGASAKI, A., ISHIMORI, A., MASAMUNE, O. and YAMAGATA, Su. Response of Lower Esophageal Sphincter Pressure to Beef Soup or AOC-Tetrapeptide Stimulation in Esophagitis. Tohoku J. exp. Med., 1977, 121 (1), 91-97 — In this study is intended a measurement of the pressure of the lower esophageal sphincter (LES) in resting state and after various stimuli such as beef soup and AOC-tetrapeptide in cases of healthy subjects and various diseases by means of an infused open-tip method. The following results were obtained: In the cases of esophagitis, the resting LES pressure is lower than in the cases of healthy subjects and after stimulation by beef soup or tetrapeptide the LES pressure is less elevated. Based on these observations, we concluded that there are some factors other than gastrin which make the LES pressure in the cases of esophagitis lower than in controls. — lower esophageal sphincter; AOC-tetrapeptide; gastrin

For the purpose of diagnosing esophageal lesions, a study of esophageal motility by such means as manometric methods has proved to be of great use in addition to morphological studies such as X-ray and endoscopic examination. In 1910’s the esophageal intraluminal pressure was measured by the balloon method. In recent years, however, with the development of medical electronics, an open-tip method using an electric manometer was invented. With the help of such devices a fundamental study of esophageal intraluminal pressure was carried out by Code and Schlegel (1958) and Miyakawa (1960). When applied clinically, an open-tip method was made available as one of the useful methods for clinical diagnosis of such diseases as achalasia of the esophagus, esophageal cancer, and esophageal hiatal hernia through the studies by Creamer et al. (1957), Akakura et al. (1964) and Hirashima et al. (1965). In this study, we applied the infused open-tip method in order to observe the resting LES pressure as well as the response to several stimulants and to scrutinize the LES function from the pathophysiological point of view in various diseases.

METHODS AND MATERIALS

For the purpose of examination, we used polyethylene tubes of equal nature and size, each 1 m in length and 1.5 mm in the inner diameter. Three tubes were combined into a
single assembly with an external diameter of 5 mm. Two of them were used for the measurement of the intraluminal pressure, the third for the aspiration of gastric juice as well as for the infusion of various solutions. Each of the two tubes for the purpose of recording had side orifices of 1.5 mm in the inside diameter; the distal aperture was intended for the measurement of the gastric fundic pressure, while the proximal one, made 5 cm apart from the former, was for the measurement of the LES pressure.

Distilled water was infused into the stomach with the constant rate of 0.5 ml/min so that the intraluminal pressure might be transmitted through two tubes. It was amplified by means of transducers (LP-U-0.1-350-0-II, Toyo Measuring Instrument Co., Ltd., Japan). Through the biophysiograph (180 system, San-Ei Instrument Co., Ltd., Japan), it was recorded with the rectigraph (8 S, San-Ei Instrument Co., Ltd., Japan). Pressures were recorded as cm H2O, the mean gastric fundic pressure being used as the zero reference. All subjects were examined in the supine position after an overnight fast. The tube was passed into the stomach and slowly withdrawn until it was positioned so that the distal aperture might record the fundic pressure while the proximal aperture the LES pressure. The resting pressure was measured in all subjects examined.

The plasma gastrin concentration was measured by means of radioimmunoassay of the dextran-coated charcoal method using CEA-IRE-SORIN Kit (Midori-Juji Co., Ltd., Japan) in order to investigate the correlation of the LES pressure to the plasma gastrin level (Yalow and Berson 1970).

To observe the effect of endogenous gastrin, 200 ml of beef soup containing 200 kcal was infused into the stomach through the tube. The intraluminal pressure was continuously recorded for 20 min and then for additional 40 min after ingestion of the test meal. In other occasions the effect of AOC-tetrapeptide (Nihonkayaku Pharmaceutical Co., Ltd., Japan) was studied following 20 min measurement of resting pressure. After an intravenous injection of 0.3 γ or 0.5 γ per kg of AOC-tetrapeptide was given, the intraluminal pressure was recorded for 15 min. For the statistical analysis of the variance in data given, Student’s T-test was employed.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number</th>
<th>Resting LES pressure (cm H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>20</td>
<td>13.1±1.7</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>6</td>
<td>12.5±1.4</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>5</td>
<td>12.7±1.4</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
<td>2</td>
<td>24.1±0.5†</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>1</td>
<td>12.0</td>
</tr>
<tr>
<td>Hiatal hernia without esophagitis</td>
<td>5</td>
<td>12.8±1.4</td>
</tr>
<tr>
<td>Esophagitis with hiatal hernia</td>
<td>5</td>
<td>10.2±1.2†</td>
</tr>
<tr>
<td>Esophagitis without hiatal hernia</td>
<td>5</td>
<td>10.1±0.9†</td>
</tr>
<tr>
<td>Esophagitis following Billroth-II</td>
<td>5</td>
<td>6.9±1.2†</td>
</tr>
</tbody>
</table>

All values are expressed as mean±s.d. †† Values are statistically different from the corresponding values in healthy controls at the levels of significance of 0.001<p<0.01 and p<0.001, respectively.

As shown in Table 1, the study was carried out on 20 healthy subjects and 34 patients with various diseases. 15 cases of esophagitis were divided into 3 groups of each 5 cases comprising esophagitis with hiatal hernia, esophagitis without it, and esophagitis following Billroth II gastrectomy. Subjects examined numbered 41 males and 13 females, their average age being 44.8 and 43.5 respectively.
As shown in Table 1, mean basal LES pressures in healthy subjects, gastric ulcer, duodenal ulcer, scleroderma without gastrointestinal symptoms, and esophageal hiatal hernia without esophagitis were 13.1±1.7, 12.8±1.4, 13.7±1.4, 12.0 and 12.8±1.4, respectively. These values were not significantly different from the resting LES pressure of healthy subjects. In 2 cases of Zollinger-Ellison syndrome, the resting LES pressure was 24.1±0.5 cmH₂O, which was significantly higher than that in controls (p<0.001). In contrast, in cases of esophagitis with hiatal hernia, in cases of esophagitis without it, and in cases of esophagitis following Billroth II gastrectomy, the values of the LES pressure were 10.2±1.2 (0.001<p<0.01), 10.1±0.9 (0.001<p<0.01) and 6.9±1.2 cmH₂O (p<0.001), respectively, which were significantly lower than in controls. When 15 cases of esophagitis were grouped together, the LES pressure was 9.1±1.9 cmH₂O (0.001<p<0.01).

In cases of esophagitis, the resting LES pressure and corresponding fasting plasma gastrin tended to be lower than in healthy subjects, whereas in cases of Zollinger-Ellison syndrome both of them tended to be higher than in healthy subjects.

When 200 ml beef soup was infused into the stomach, the peak LES pressures of healthy subjects and cases of esophagitis were 25.7±0.5 and 17.1±1.8 cmH₂O, respectively. The peak percentage response to the resting LES pressure was 221.0 ±4.2 and 180.5±10.5%. This implies that the peak LES pressure and the peak percentage response in the LES pressure of the cases of esophagitis were lower than in healthy subjects. The peak LES pressure and the peak percentage response in the LES pressure after administration of 0.3 γ/kg or 0.5 γ/kg of AOC-tetrapeptide were noted to be lower in esophagitis than in controls just as after beef soup administration (Table 2).

### Table 2. Resting LES pressure and peak response in LES pressure to beef soup and AOC-tetrapeptide stimulation in healthy subjects and cases of esophagitis

<table>
<thead>
<tr>
<th>Methods of stimulation</th>
<th>Subjects</th>
<th>Number</th>
<th>Resting LES pressure (cm H₂O)</th>
<th>Peak response in LES pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef soup 200 ml (200 kcal)</td>
<td>Healthy subjects</td>
<td>3</td>
<td>12.2±0.5</td>
<td>25.7±0.5; 211.0±4.2;</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
<td>3</td>
<td>9.5±0.5</td>
<td>17.1±1.8; 180.5±10.5;</td>
</tr>
<tr>
<td>AOC-tetrapeptide 0.3 γ/kg i.v.</td>
<td>Healthy subjects</td>
<td>6</td>
<td>13.1±0.5</td>
<td>19.4±0.5*; 148.1±12.5*</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
<td>6</td>
<td>10.4±1.0</td>
<td>12.6±3.0; 121.2±15.0</td>
</tr>
<tr>
<td>AOC-tetrapeptide 0.5 γ/kg i.v.</td>
<td>Healthy subjects</td>
<td>6</td>
<td>14.0±1.2</td>
<td>25.8±3.5; 184.3±16.3;</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
<td>6</td>
<td>10.6±1.0</td>
<td>13.7±3.2; 129.2±14.5</td>
</tr>
</tbody>
</table>

All values are expressed as mean±S.D. and statistical differences are calculated between resting LES pressure and peak response in LES pressure in healthy subjects and cases of esophagitis. *‡ Values are statistically different from the corresponding values in healthy controls at the levels of significance of 0.01<p<0.02 and p<0.001, respectively.
Fig. 1. LES pressure response curve after administration of beef soup in each 3 cases of healthy subjects and esophagitis. ••••, healthy subjects; ••••, esophagitis. •••• Values are lower than the corresponding values in healthy subjects at the levels of significances of 0.01<p<0.02, 0.001<p<0.01, and p<0.001, respectively.

Fig. 2. LES pressure response curve after administration of 0.5 γ/kg of AOC-tetrapeptide in each 6 cases of healthy subjects and esophagitis. ••••, healthy subjects; ••••, esophagitis. •••• Values are lower than the corresponding values in healthy subjects at the levels of significances of 0.01<p<0.02, 0.001<p<0.01, and p<0.001, respectively.

Figs. 1 and 2 show the changes of the LES pressure in the cases of healthy subjects and esophagitis in response to the administration of beef soup and 0.5 γ/kg AOC-tetrapeptide, respectively. In the cases of esophagitis, the rise of LES pressure to the stimulation of either beef soup or AOC-tetrapeptide was much less distinct in comparison with that in the healthy subjects.

DISCUSSION

It has been reported that the barrier to reflux at the gastroesophageal junction depends upon the intrinsic strength of the LES and that this intrinsic strength of the LES is closely correlated to the results of infused intraluminal manometry.
Lower Esophageal Sphincter Pressure

(Cohen and Harris 1970). The resting LES pressure of our cases of esophagitis showed low values compared with that of healthy subjects. This may imply the decrease of intrinsic strength of the LES in esophagitis, which is supposed to be one of the main causes of reflux often accompanying this clinical entity.

As the possible factors that control the strength of LES, the following gastrointestinal hormones have been postulated: gastrin (Cohen 1972), secretin (Cohen and Lipshutz 1971), CCK-PZ (Resin et al. 1973) and glucagon (Jaffer et al. 1974). Roles of cholinergic innervation of the LES (Roling et al. 1972) and smooth muscle comprising the LES (Lipshutz et al. 1973) have also been proposed. Giles et al. (1969) confirmed that gastrin and pentagastrin elevate the LES pressure, that the administration of atropine abolishes this increase, and that even meat extract can elevate the LES pressure. Castell and Harris (1970) suggested that, in view of the fact that alkali infused into the stomach causes an increase of the LES pressure, endogenous gastrin might play an important role in the stimulation of the LES muscle. They further hinted that the regulation of the LES pressure depends upon the physiologic action of gastrin, because a marked increase of the LES pressure is observed after subcutaneous injection of gastrin-like pentapeptide. Later, Lipshutz et al. (1972) succeeded in demonstrating that endogenous gastrin is the major determinant of the resting LES pressure on the basis of the finding that the administration of rabbit gastrin antiserum upon the opposum causes the inhibition of the LES pressure of this animal by 80.0±3.1%. Nebel and Castell (1972) suggested that the release of gastrin from the gastric antrum might determine the LES pressure because the LES pressure elevates after protein meal while acid inhibits it, although they did not measure the blood gastrin levels directly. Furthermore, Isenberg et al. (1971) noticed that in cases of Zollinger-Ellison syndrome there is a significant correlation between LES pressure and plasma gastrin. Hence we may safely assume that gastrin is a major factor that regulates the LES pressure.

In our study, too, the general tendency is that the cases of esophagitis show lower gastrin levels than did controls, whereas the cases of Zollinger-Ellison syndrome show higher levels. Concomitantly, the former cases tend to show lower LES pressures; in contrast, the latter cases tend to show higher values. This may make the assumption possible that there is some correlation between endogenous gastrin and LES pressure. In order to clarify this point, we compared the changes in LES pressure after administering beef soup and tetrapeptide in the cases of esophagitis and controls.

Lipshutz et al. (1974) confirmed that the administration of pentagastrin to the patients with esophagitis does not make the response curve of the LES pressure different from that of controls, while the administration of glycine to the patients with esophagitis does make it different from controls. He interpreted that the diminished response in LES pressure is due to insufficient release of gastrin after infusion of alkali or glycine into the stomach of the patients with esophagitis. On the contrary, Farrell et al. (1974) reported that in the cases of esophagitis the LES
pressure increases less than in controls after administration of either protein meal or pentagastrin. He assumed that pharmacological doses of pentagastrin should result in an elevation of serum levels of gastrin-like activity many times in excess of those occurring under physiological conditions and came to the conclusion that gastrin is not the only factor responsible for esophageal sphincter incompetence in cases of esophagitis. Through our study, we reached the result similar to that of Farrell et al. Namely, in cases of esophagitis, the peak response to graded doses of tetrapeptide is lower than in controls both in terms of absolute value and of percentage of the resting pressure. Equally, the peak response to beef soup infused into the stomach is lower in cases of esophagitis than in controls.

Through these observations, we conclude that there are some factors other than gastrin which make the LES pressure in the cases of esophagitis lower than in controls, and that, although the diminution of the gastrin release is perhaps one of the factors of esophageal sphincter incompetence in esophagitis, it is certain that there is some functional abnormality in the sphincter itself, which causes the diminution of sensitivity of LES to gastrin.

References


