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Correlation between Plasma Gastrin and Antral G Cell after Esophagectomy

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Introduction

During total esophagectomy, bilateral truncal vagotomy was performed. Our interest was aroused as to how this changed the intrathoracic stomach. It has been said that postoperative hypergastrinemia occurs after all types of vagotomy: truncal vagotomy^{2,13,23}, selective vagotomy^{7,12,18}, or selective proximal vagotomy^{3,14,17}. There have been many reports^{6,8,11} on the causes of hypergastrinemia, but there is no agreement. This paper describes our investigation of the postoperative secretion of plasma gastrin and secretin in patients with esophageal cancer, along with endoscopic observations of G-cells.

Materials and Methods

The subjects of this study were 14 male and female patients with esophageal cancer aged 52 to 80 years, and 7 healthy persons aged 50 to 70 years.

1) Operative procedure

After right thoracotomy and laparotomy, total esophagectomy was performed, followed by esophageal reconstruction by lifting the entire stomach into the thorax by the posterior mediasternal route.

2) Plasma gastrin level after oral glucose load

After an over-night fast, blood was collected from the antecubital vein of the 7 controls and 14 patients with esophageal cancer (all 14 preoperatively, 8 at one month, and 6 at more than 3 months after surgery). All the subjects were given 50 g of glucose orally and blood was drawn 15, 30, 60, 90 and 120 minutes later to determine the plasma gastrin level. Gastrin was measured

Key words: Plasma gastrin, Plasma secretin, Gastrin secreting G Cell, PAP method.

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by the charcoal-dextran method with CIS kits. Statistical analysis was performed by either student's t-test or the paired t-test.

3) Oral 0.1N HCl test

Preoperatively and one month after operation, blood was taken from the antecubital vein of 6 patients with esophageal cancer after an over-night fast. Then 50 ml of 0.1N HCl was given orally, and blood was collected 5, 15, 30, and 60 minutes later and placed into a cooled sedimentation tube containing Aprotinin, 1,000 units/1 ml blood. It was centrifuged at 3,000 r.p.m. for 15 minutes at temperatures below 4°C, then frozen and stored at -20°C. The secretin level was determined by the double antibody method.

4) Gastric acid examination

Preoperatively and one month after surgery, gastric juice was collected from the patients with esophageal cancer after an over-night fast, 60 minutes before and at intervals of 10 minutes for 1 hour after the administration of 4 µg/kg of tetragastrin. The volume and total acidity of the gastric juice were measured, and BAO and MAO were calculated.

5) G-cell stain by the enzyme antibody method

In 8 patients with esophageal cancer, endoscopic biopsy was performed postoperatively of the greater curvature of the pyloric part of the stomach. The tissues removed were immediately fixed in neutral formalin and embedded in paraffin within 48 hours. The paraffinized slices were then deparaffinized with an organic solvent such as xylene, and ethanol and water were added. The slices were dipped in TBS (pH 7.6, 0.05M Tris buffer solution) and stained by the following 6 steps with PAP kits of DAKO (22 F North Milpas street, santana Barbara, CA 93130, USA).

Step 1: 3% H_2O_2 solution. After the removal of excess water, a slice was entirely covered with several drops of 3% H_2O_2 in bottle 1 and allowed to react at room temperature for 5 minutes. Then the slice was put in TBS for 5 minutes.

Step 2: After excess water had been wiped off with absorbent paper, the slice was put in NSS for 20 minutes, and the water was again wiped off.

Step 3: The first antibody was dropped onto the slice and allowed to stand for 20 minutes. Then the slice was placed in TBS for 5 minutes.

Step 4: After the moisture had been wiped off with absorbent paper, the second antibody was dropped onto the slice and allowed to stand at room temperature for 20 minutes.

Step 5: Moisture was blotted away again, and PAP was dropped onto the slice and allowed to react at room temperature for 20 minutes. The tissue was placed in TBS for 20 minutes.

Step 6: A substrate solution was prepared by dropwise addition of hydrogen peroxide to 20 ml of the buffer. Water was wiped away with absorbent paper, and the substrate solution was dropped onto the slice, which was allowed to stand at room temperature for 20 minutes. The slice was then washed with tap water, and placed in Mayer's hematoxylin for minutes. The slice was again washed with tap water for 15 minutes and sealed in glycerin and covered with a cover glass.

Results

1. Changes in plasma gastrin levels after oral glucose (Table 1)

The mean plasma gastrin level of the control group was 84 ± 29 pg/ml fasting, and 128 ± 60 ($p < 0.05$), 103 ± 35 , 86 ± 30 , 86 ± 33 , and 84 ± 31 pg/ml 15, 30, 60, 90 and 120 minutes, respectively, after glucose administration; i.e., increased levels. The mean preoperative plasma gastrin level of the patients with esophageal cancer changed from the fasting level of 59 ± 17 pg/ml to 83 ± 30 ($p < 0.05$), 74 ± 27 , 67 ± 19 , 66 ± 20 , and 58 ± 14 pg/ml 15, 30, 60, 90 and 120 minutes, res-

Table 1. Changes of plasma gastrin levels after glucose load before and after surgery

	Patients	Time					
		No	0	15	30	60	90
Control plasma gastrin levels (pg/ml)	1	62	42	73	65	54	56
	2	132	138	93	74	64	61
	3	118	182	142	140	157	150
	4	55	111	48	49	67	57
	5	96	240	163	115	100	103
	6	55	100	80	62	68	70
	7	70	86	124	96	93	90
	Means	84	128	103	86	86	84
±SEM	29	60	35	30	33	31	
Pre-operative patients plasma gastrin levels (pg/ml)	1	85	125	92	73	74	61
	2	50	64	47	46	50	51
	3	50	95	50	55	57	53
	4	60	70	78	74	76	60
	5	25	28	33	32	32	28
	6	63	66	75	71	91	68
	7	62	120	111	98	67	65
	8	80	99	107	89	83	80
Means	59	83	74	67	66	58	
±SEM	17	30	27	19	20	14	
One month after surgery plasma gastrin levels (pg/ml)	1	500	585	568	421	378	394
	2	258	279	200	160	183	179
	3	342	483	281	220	193	250
	4	147	150	121	78	75	76
	5	147	246	178	130	136	228
	6	499	391	262	199	162	257
	7	193	198	166	140	123	122
	8	276	487	431	394	88	88
Means	296	352	276	218	167	199	
±SEM	133	147	142	156	89	99	
Three months after surgery plasma gastrin levels (pg/ml)	1	70	96	78	54	54	56
	2	62	83	58	47	40	52
	3	76	79	61	40	55	42
	4	77	166	109	62	53	48
	5	294	269	194	172	139	169
	6	172	212	272	258	231	277
	Means	125	151	129	106	95	107
	±SEM	72	72	79	82	69	88

Table 2. Correlation between basal gastrin level and pyloroplasty, one month after surgery

Patients	Plasma gastrin levels after one month after surgery							
	I, T	O, O	T, S	H, K	W, S	K, K	I, M	K, M
Basal gastrin pg/ml	500	258	342	147	147	499	193	276
Pyloroplasty	+	-	-	-	+	-	-	-

pectively, after glucose administration ; i.e. increased levels. While the corresponding figures in the same patients one month after surgery were 296 ± 133 fasting and 352 ± 147 ($p < 0.05$), 276 ± 142 , 218 ± 156 , 167 ± 89 and 199 ± 99 pg/ml after glucose administration ; i.e. increased levels. Three months after surgery, the values were 125 ± 72 , 151 ± 72 , 129 ± 79 , 106 ± 82 , 95 ± 69 and 107 ± 88 pg/ml, respectively. These results indicate that hypergastrinemia was present one month after surgery, but that gastrin levels then tended to return to normal. It was also concluded that there was no correlation between the fasting gastrin level one month after surgery and the practice of pyloroplasty (Table 2).

Of the eight patients examined more than 3 months after surgery, 3 had chronic gastritis, one had gastric ulcer one gastric erosion, and 3 were normal.

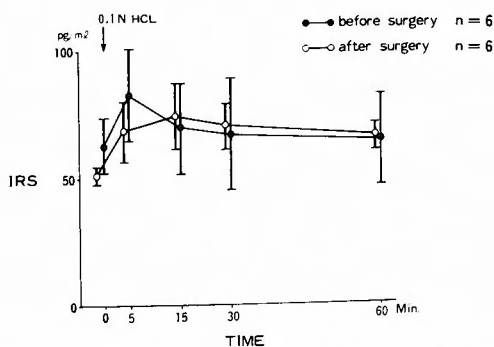
2. Changes in plasma secretin levels after oral 0.1 N HCl (Fig. 1)

The mean preoperative plasma secretin level of the patients with esophageal cancer was 63 ± 11 pg/ml fasting, and 83 ± 17 , 70 ± 18 , 67 ± 22 , and 65 ± 18 pg/ml at 5, 15, 30 and 60 minutes, respectively, after HCl administration.

One month after surgery, the values in the same patients were 51 ± 3 fasting, 69 ± 12 , 75 ± 13 , 71 ± 9 and 67 ± 5 pg/ml at 5, 15, 30 and 60 minutes, respectively. These data reflect a tendency for the plasma secretin level to decrease postoperatively, but the differences are not statistically significant.

3. Gastric secretion (Fig. 2)

In the patients with esophageal cancer, BAO and MAO were 4 ± 3 and 9 ± 4 mEq/h, respectively, preoperatively and 0.008 ± 0.001 and 0.29 ± 0.19 mEq/h, respectively postoperatively. Truncal vagotomy thus caused a great decrease in gastric secretion.

**Fig. 1.** Changes of plasma secretin levels before and after surgery

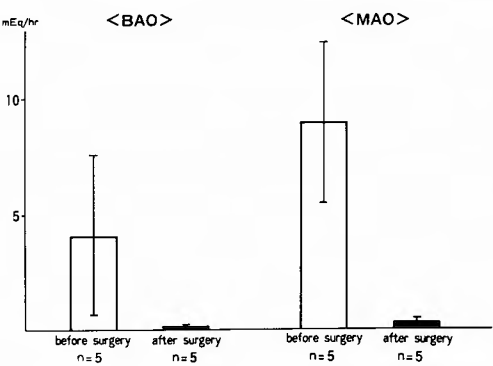


Fig. 2. Changes of basal and maximal acid output before and after surgery

4. Study of G-cell by PAP stain (Fig. 3)

Endoscopic biopsy of the pyloric part of the stomach was performed in 6 patients after esophagectomy; the removed tissue was fixed immediately in neutral formalin, embedded in paraffin, and stained with PAP solution.

Through a light microscope (objective, 10 x ; ocular, 10 x), photos of G-cells were taken.



Fig. 3. Hyperplasia of antral G-cells after surgery

Disucussion

In the surgical treatment of esophageal cancer, it is considered that bilateral truncal vagotomy is unavoidable and that it has some effect on the intrathoracic stomach. Hypergastrinemia following truncal vagotomy has been reported, but there has been much controversy about its causes. To determine the main cause, we compared the preoperative and postoperative secretion of plasma gastrin and G-cell populations, and the secretion of plasma secretin, a gastrin secretion inhibiting hormone. Fig. 1 shows changed in the plasma gastrin level after the surgical treatment of esophageal cancer. Preoperatively, plasma gastrin levels were within the normal range, although it had been thought that plasma gastrin secretion would be depressed in these patients with esophageal cancer because of reduced food intake. One month after surgery, the plasma gastrin levels were increased, both the basal levels and the response to oral glucose administration. Three months after operation, however, the plasma gastrin levels were lowered to nearly the control values, both the basal levels and the response to glucose. The causes of hypergastrinemia appearing after vagotomy, as reported in a number of studies are listed as follows: 1: interruption of a negative feed back mechanism due to a vagotomy-induced decrease in acid secretion, 2: gastric stasis associated with vagotomy, 3: adrenal hyperfunction, 4: decreased antigastrin hormone secretion, 5: hyperplasia and/or hyperfunction of G-cells, and 6: the others. The presence of a negative feed back mechanism (1) is supported by our finding that acid secretion was markedly reduced, as shown in Fig. 3, (2) has been suggested by many researchers^{6,8,11} who studied gastric emptying by ⁹⁹mTc and its relationship to plasma gastrin levels after vagotomy. JAFFE et al.¹² reported that selective proximal vagotomy without pyloroplasty prolonged the gastric emptying time and increased plasma gastrin secretion. On the other hand, KORMAN et al.¹⁵ found no difference in plasma gastrin secretion after parietal cell vagotomy with and without pyloroplasty. HANSKY⁹ and BRANDSBORG et al.⁹ independently reported that hypergastrinemia was not improved by the addition of pyloroplasty. DONAVAN et al.⁵ also noted no correlation between plasma gastrin and gastric emptying after vagotomy. As shown in Tables 2, our results also showed hypergastrinemia whether or not pyloroplasty was performed. This may be attributed to adrenal hyperfunction (3) induced by operative invasion. STADIL et al.¹⁹ examined the plasma gastrin level and gastric acid output after administration of epinephrine and found a significant increase in plasma gastrin. As to (4), although postoperative plasma secretin was more likely to be depressed than preoperative secretin, as shown in Fig. 2, the difference between the two was not significant. This finding was consistent with that of WARD et al.²⁴, who administered hydrochloric acid into the duodenum of healthy persons, patients with duodenal ulcer and those undergoing truncal vagotomy, selective vagotomy or selective proximal vagotomy and noted that secretin was sufficiently retained in all patients; secretin secretion did not depend upon the vagal nerve. As to (5), our study provides evidence of elevated plasma gastrin levels and hyperplasia of antral G-cells without antral mucosal atrophy (Fig. 3).

Patients with antral mucosal atrophy showed decreases in antral G-cells despite high plasma gastrin levels. In such cases, gastrin was thought to be secreted by duodenal G-cells, as STERN²¹

and HAYES et al.¹⁰⁾ proposed. The association of hypergastrinemia with the G-cell population has been investigated by numerous researchers using electron microscopy, fluorescent antibody techniques, or enzyme antibody methods. ASNAES¹⁾, and POLAK et al.¹⁶⁾ reported a positive correlation between the G-cell population in the antral mucosa and the plasma gastrin level on the basis of their comparative study of endoscopic biopsies of normal persons and patients with duodenal ulcer or atrophic gastritis. On the contrary, STAVE²⁰⁾ and Crivell et al.⁴⁾ reported no correlation between G-cell population and plasma gastrin levels. STOCKBRUGGER et al.²²⁾ performed endoscopic antral biopsies in patients with hypochlorhydria and reported hyperplasia of the G-cell population and hypergastrinemia in patients with atrophic gastritis of the corpus but normal antral mucosa, whereas hypoplasia of the G-cell population and hypogastrinemia were noted in patients with hypertrophic antral mucosa. In our study, we could not find correlation between G-cell populations and plasma gastrin levels but we should be further examined duodenal mucosa.

Summary

- 1) Hypergastrinemia developed one month after surgery, but 3 months or more after surgery, the plasma gastrin level was close to normal.
- 2) Plasma secretin levels tended to fall postoperatively, but not to a statistically significant degree.
- 3) Staining by the enzyme antibody method revealed hyperplasia of G-cells in patients with hypergastrinemia without pyloric antral atrophy although other hypergastrinemic patients had a decrease in G-cells due to pyloric antral atrophy. In the latter cases, gastrin was thought to be secreted from the duodenum.

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和文抄録

食道癌手術後、再建胃の幽門前庭部のガストリン 分泌細胞と血中ガストリン値について

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食道癌患者，術前 8 名，術後 1 カ月 8 名，術後 3 カ月以上 6 名にトレラン G 150 ml を経口負荷し，血清ガストリンを検索するとともに，術前，術後 1 カ月に 0.1 規定塩酸を経口負荷し，血清セクレチン分泌動態を検索した。さらに内視鏡的に術後胸腔内胃の幽門前庭部の生検を行い，酵素抗体法（PAP）にてガストリン分泌細胞を検索し，血清ガストリンとの相関関係について検討を加え，以下の知見を得た。

1) 術後 1 カ月では高ガストリン血症を来したが術後 3 カ月以上では，血清ガストリン値は，正常範囲近くに低下した。

2) 血清セクレチン値は，術後低下する傾向を認めたが，統計学的有意差を認めなかった。

3) 酵素抗体法によるガストリン分泌細胞の検索では，高ガストリン血症を来すもので幽門前庭部に萎縮，腸上皮化生の見られないものでは，ガストリン分泌細胞の過形成がみられたが，幽門前庭部に萎縮，腸上皮化生を来し，ガストリン分泌細胞が減少しているにもかかわらず，高ガストリン血症を来す症例も認めた。これらの症例では，肝機能，腎機能が正常であった事より，おそらくガストリンは十二指腸から分泌されているものと考えられる。