Plasma Gastrin and Cholecystokinin Response After Pylorus-preserving Pancreatoduodenectomy with Billroth-I Type of Reconstruction

AKIRA TANGOKU, M.D., MASAHIRO NISHIKAWA, M.D., ATSUSHI ADACHI, M.D., and TAKASHI SUZUKI, M.D.

From the Department of Surgery II, Yamaguchi University School of Medicine, Ube, Japan

Plasma gastrin and cholecystokinin (CCK) responses were measured after a pancreatoduodenectomy (PD) using the Billroth-I type reconstruction combined with distal partial gastrectomy (standard PD) and combined with preservation of the pylorus and the duodenal bulb (PPPD). Six unoperated patients, 4 men and 2 women, were studied as control subjects. Basal plasma levels of gastrin were significantly higher in controls than in patients who had a standard PD ($p < 0.05$) and gastrin responses to a meal were also blunted in these patients. In contrast basal and postprandial levels of gastrin after PPPD were significantly higher than these found in patients with standard PD ($p < 0.05$). Postprandial gastrin response after PPPD were similar in pattern to these found in controls. Integrated gastrin release after PPPD was less than that of the control but was significantly greater than that in patients with standard PD. Basal plasma levels of CCK in the patients after the standard PD were significantly lower than in controls and significantly higher postprandial levels of CCK were found after PPPD compared to standard PD ($p < 0.05$). However integrated CCK from 0 to 120 minutes were not significantly different between PPPD and standard PD groups. Based on these observations concerning hormonal release of gastrin and CCK, preservation of the stomach and the duodenal bulb appears to be a more physiologic reconstructive procedure than the standard PD. In addition the operation probably has more beneficial effect on the injured pancreas in time.

GASTRIN AND CCK are the important gut hormones that have pancreatotrophic action and an important role in the regulation of exocrine and endocrine function of the pancreas.[1-5] Pylorus-preserving pancreatoduodenectomy (PPPD) is a surgical procedure of reconstruction that preserves the gastrointestinal function after a pancreatoduodenectomy (PD).[6] We performed a new type of reconstruction[7] in which we resected a minimal area of duodenum preserving the neurovascular supply of the pylorus and the duodenal bulb (PPPD).

Gastric acid release, gastric emptying, and marginal ulcer formation have been reported after PPPD.[8-11] However there are few reports concerning hormonal changes in gastrin and CCK in these PPPD patients. These hormones accelerate functional and morphologic regeneration of the residual pancreas when comparisons are made before and after PD. In this study we compared basal and postprandial levels of gastrin and CCK between PPPD, standard PD group, and control.

Materials and Methods

From April 1987 through August 1989, 33 patients underwent PD procedure in our department, of whom PPPD was done for 15 patients and the standard PD was for 18 patients. Both PPPD and standard PD were reconstructed with the Billroth-I method (Fig. 1). Seven patients (3 men, 4 women), ranging in age from 34 to 72 years (mean, 48.8 years) who had the PPPD were examined. The final diagnosis of these patients was chronic pancreatitis in 2, common bile duct cancer in 2, pancreatic cyst in 2, and islet tumor in 1. Six of the patients (1 men, 5 women) ranging in age from 42 to 75 years (mean, 56.7 years) who had undergone standard PD also were examined. This final diagnosis for them was five with pancreatic head cancer and one with common bile duct cancer. These patients were free of recurrence of disease at the time of the study.

The control group consisted of six patients (four men, two women), ranging in age from 18 to 75 years (mean, 40.3 years). Three of them suffered from chronic pancreatitis, one with congenital pancreatic cyst, and two were normal volunteers. They had not been operated on before this study. A test meal was given to PPPD patients 1 to 11 months (mean, 5.1 months) and to PD patients 2 to 5 months (mean, 4.1 months) after surgery.

After an overnight fast, a catheter was inserted into a peripheral vein to collect blood samples. Each patient was

Address reprint requests to Akira Tangoku, Department of Surgery II, Yamaguchi University School of Medicine, 1144 Kogushi, Ube 755, Japan.

Accepted for publication August 21, 1990.

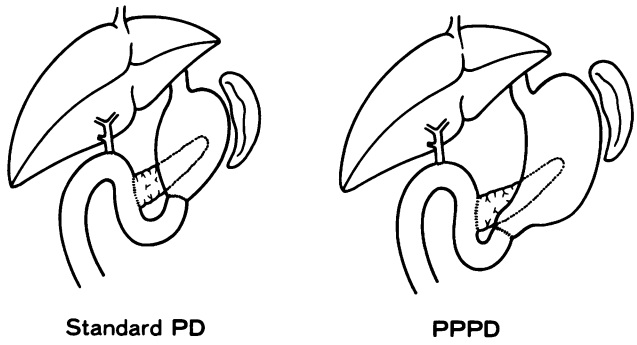

FIG. 1. Schema of two types of reconstruction with Billroth-I method after pancreatoduodenectomy.

given 250 mL of a liquid meal (YH-80 consisting of 7.75 g of protein, 6.5 g of fats, and 40.35 g of glucose, Meiji Milk Products Co., Ltd., Tokyo, Japan), and blood samples were collected for gastrin and CCK assays at 10-minute intervals before and for 120 minutes after the meal.

Blood Collection

Blood samples were collected with or without heparin (10 U/mL) and Trasylol (50 KIU/mL), maintained on ice, and plasma separated by centrifugation at 4°C and 3000 rpm for 15 minutes. Plasma was stored at −80°C for subsequent assay of gastrin and CCK by radioimmunoassay (RIA).

Radioimmunoassays

Gastrin. Blood samples were collected without heparin and plasma separated by centrifugation. Plasma gastrin was measured using a CIS gastrin radioimmunoassay kit (Gastrin RIA Kit II, Dinabot, Japan).

CCK. Blood samples for CCK were collected in tubes containing 10 U/mL of heparin and 50 KIU/mL of Trasylol. Plasma concentration of CCK was measured by radioimmunoassay using a specific antibody (specific to CCK-33 [100%], CCK-8 [100%], CCK-39 [84.6%], gastrin [0%]). The details of this method has been published previously.[12,13]

Dual Scintigraphy

During a 12-hour fast, the patients who had PD (standard PD or PPPD) were positioned semirecumbent in front of a large field of view gamma camera (Digital gamma camera GCA-A/W2, Toshiba, Tokyo, Japan) fitted with a diverging collimator (Toshiba medium energy general purpose collimator model ROC-930A) on line to a scintigraphic data analyzer (Toshiba medical image processor model GMS-550J). One hundred eighty-five MBq of ^{99m}Tc-N Pyridoxyl-5 methyl tryptophan (^{99m}Tc-PMT) was administered from the peripheral vessel before each patient was given 60 g of semiliquid meal containing 10 g of Clinimeal (Eisai Co., Tokyo, Japan) labeled with 37 MBq of ^{111}In-diethylene triaminepentaacetic acid (^{111}In-DTPA). Both agents were imaged by using the two windows on the gamma camera by every 1 minute for 45 minutes and all data were stored in computer. Time activity curve was calculated by counting the percentage radioactivity of maximum in the area of the upper small intestine.

Statistical Evaluation

The results are expressed as mean ± SE, and ANOVA with Newman-Keuls test and independent student t test (for comparison of the integrated values) were used to evaluate statistical significance. A probability value of less than 0.05 was considered significant.

Results

Measurement of Plasma Levels of Gastrin

Postprandial plasma gastrin responses in control patients after standard PD and after PPPD are shown in Figure 2. In standard PD patients, the basal level of gastrin was significantly lower than the control ($p < 0.05$), but there was no significant difference between PPPD patients and the control. In controls plasma gastrin increased from a mean fasting value of 70.1 ± 11.8 pg/mL to 130.7 ± 23.5 pg/mL at 20 minutes after the meal. In the post-PPPD patients, plasma gastrin also increased from 48.2 ± 5.9 pg/mL to 76.6 ± 10.2 pg/mL at 20 minutes after the meal. There was little or no postprandial gastrin release in the standard PD patients and gastrin levels were significantly less than PPPD patients and control throughout the entire time course ($p < 0.05$). Integrated gastrin release (0 to 120 minutes) in the control was 3267.7 ± 1062.6 pg/min/mL, 2092.1 ± 500 pg/min/mL in the PPPD group and 290.4 ± 122 pg/min/mL in the standard PD group, a value significantly less than that of the control and of

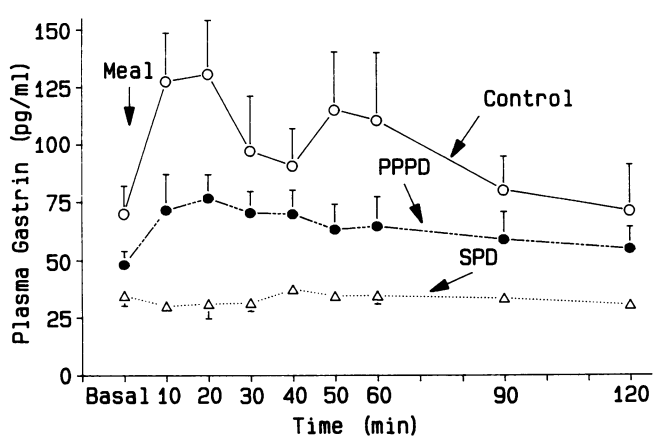

FIG. 2. Comparison of gastrin response after the test meal in control group (n = 5) to standard PD (n = 6) and PPPD (n = 6) procedures. Data are expressed as mean ± SE. There was a significant difference ($p < 0.05$) between standard PD and PPPD groups throughout the time course.

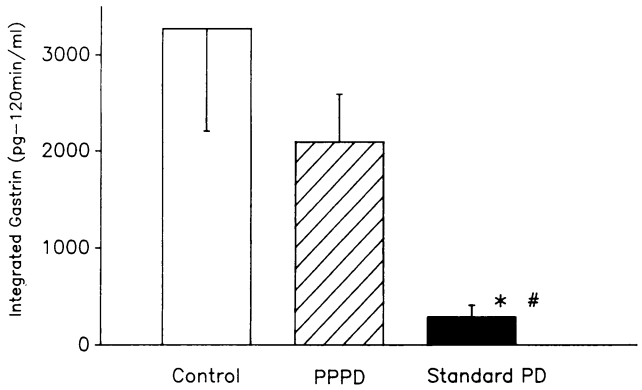

FIG. 3. Integrated gastrin (120 minutes) in control, standard PD, and PPPD groups. Data are expressed as mean ± SE. Asterisk indicates a significant difference ($p < 0.05$) between standard PD and PPPD groups. Sharp sign indicates a significant difference ($p < 0.01$) between standard PD and control.

PPPD patients. There was no significant difference between PPPD and control (Fig. 3).

Measurement of Plasma Levels of CCK

Basal CCK level was 7.0 ± 1.0 pg/mL in the control group, 7.0 ± 2.2 pg/mL in the PPPD group and 1.2 ± 0.8 pg/mL in the standard PD group. Peak response of CCK was 24.0 ± 13.3 pg/mL in the control group at 20 minutes, 15.1 ± 3.4 pg/mL in the PPPD at 30 minutes, and 8.0 ± 4.8 pg/mL in the standard PD at 30 minutes. All peak concentrations were significantly higher than the basal levels ($p < 0.05$).

Basal and postprandial CCK levels in the standard PD group were significantly lower than the control group ($p < 0.05$), whereas postprandial CCK levels were significantly higher in the PPPD group as compared to the standard PD group ($p < 0.05$) (Fig. 4). Cholecystokinin release pattern in PPPD resembled the control and no significant difference between PPPD and control was found.

The integrated CCK response from 0 to 120 minutes was 390.3 ± 225.6 pg/min/mL in the control group, 424.8 ± 157.5 pg/min/mL in the PPPD, and 267.1 ± 92.6 pg/min/mL in the standard PD group. There was no significant difference between the control, PPPD, and standard PD patients (Fig. 5).

Dual Scintigraphy

Dual scintigraphy with ^{99m}Tc-PMT- and ^{111}In-DTPA-labeled food showed complete and gradual mixing of bile and food in both standard PD and PPPD (Fig. 6). Standard PD showed slightly incomplete mixing of bile and food, but this difference was not found significant.

Discussion

Pancreatoduodenectomy is a procedure that resects the gallbladder, the distal part of the stomach, the entire duodenum, the proximal jejunum, and the head of the pancreas. These portions contain many different kinds of gut hormone-releasing cells, which have important roles in the regulation of gastric acid secretion and metabolism of glucose, protein, and fat. Traverso and Longmire[6] suggested that PPPD with Billroth-II type reconstruction could prevent dumping and other postoperative symptoms as well as maintain weight gain. We[7] performed a new PPPD with Billroth-I type reconstruction and reported that this operative procedure has several advantages over others in that it preserves gut hormonal status.[9]

In the current study we found that fasting plasma gastrin levels were highest in the control and lowest in the standard PD group and that PPPD patients had significantly higher gastrin levels than standard PD. The postprandial gastrin response pattern after PPPD resembled that of the control, as has been reported previously.[9] It is of interest that plasma levels of gastrin in standard PD did not in-

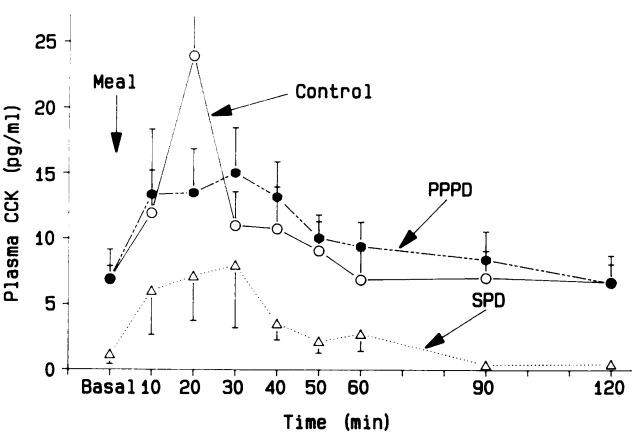

FIG. 4. Comparison of CCK response to the test meal in control (n = 5), standard PD (n = 5), and PPPD (n = 5) groups. Data are expressed as mean ± SE. There was a significant difference ($p < 0.05$) between standard PD and PPPD groups through the entire time course. No significant difference was found between PPPD and control.

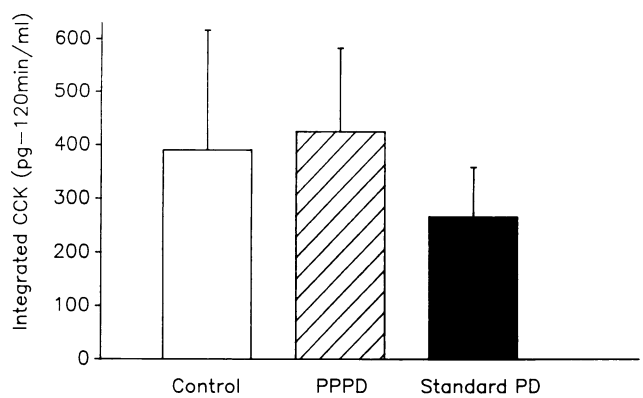

FIG. 5. Integrated CCK (120 minutes) in control, standard PD, and PPPD groups. Data are expressed as mean ± SE. No significant differences were found among control, PPPD, and standard PD groups.

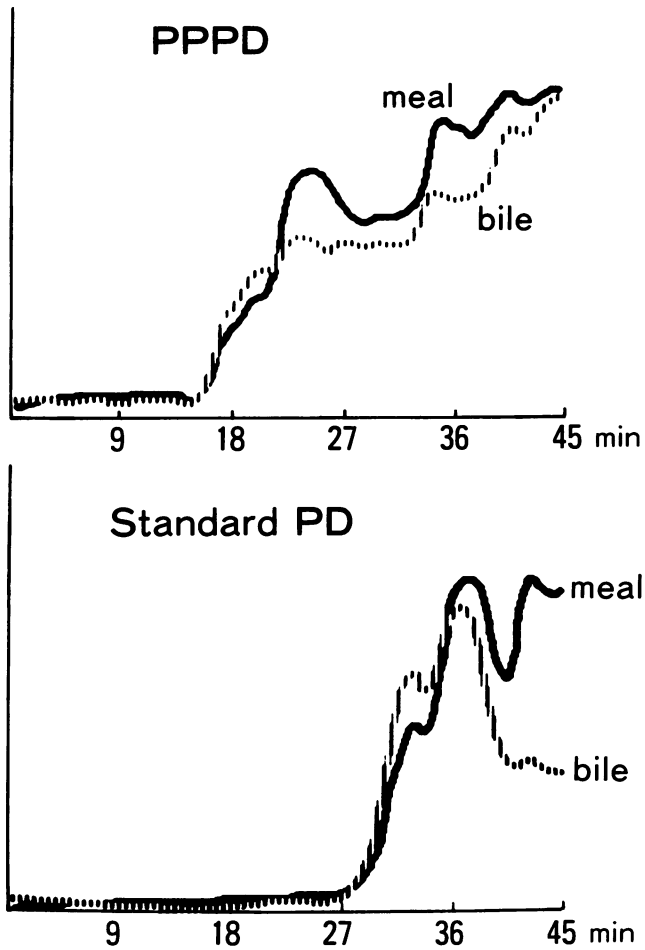

FIG. 6. Time activity curves of dual scintigraphy. Time activity curves were calculated by counting the percentage of maximam radioactivity of ^{99m}Tc-PMT and ^{111}In-DTPA. They showed complete mixture of bile and food both in PPPD and standard PD. No significant difference was found between them.

crease after a meal. Sato et al.[14] also reported that plasma gastrin levels of the patients with Whipple's reconstruction after PD were remarkably reduced after the surgery. Because the normal antrum and bulb are richly populated with gastrin-releasing cells, our results and those of others that show low levels of gastrin after PD suggest that this postoperative phenomenon may be due to the lack of hormone-releasing cells.

Total CCK release in PPPD patients was significantly larger than that of patients with standard PD, whereas postprandial response of CCK was similar to that found in controls. Several factors in PD patients may play a role in alternation of plasma CCK levels. Gastrectomy is one of them. It was reported that patients with gastrectomy, especially in Billroth-II anastomoses, have an impaired release of CCK[15] and an increased incidence of gallstones.[16] Satake and colleagues[17] measured endogenous CCK release after a test meal in controls and in patients with Billroth-I and Billroth-II anastomoses after subtotal gastrectomy and reported that 2 months after the surgery postprandial plasma levels of CCK were similar to the controls. Hopman[18] showed that the mean fasting plasma CCK in patients after gastrectomy was similar to that in controls; however CCK responses to oral fat in the patients after gastrectomy were significantly greater than the control patients. Becker et al.[19] also reported that basal CCK concentrations were not altered after Billroth-I or Billroth-II gastric resections but they reported that a significant increase in plasma CCK levels immediately after food. It has been suggested that the increase in CCK levels after gastrectomy was due to vagotomy and rapid gastric emptying, which results in activation of a large number of food-stimulated CCK cells.[17,18] However Guzman and colleagues[20] and Fried and colleagues[21] found that CCK release is not under vagal control. Thus the effect of gastrectomy to CCK release is still controversial.

Pancreatoduodenectomy is the procedure that resects gallbladder, duodenum, and the upper part of jejunum and stomach. Postprandial CCK levels in the standard PD group in this study were significantly lower than in the controls and PPPD group. Ogden et al.[22] reported that the concentration of CCK-releasing cells is highest in the duodenum and progressively diminishes distally in the small intestine. Lower CCK levels after PD may be due to resection of the duodenum and jejunum, where the concentration of CCK releasing cells is richest.

Basal and postprandial CCK levels were significantly higher in PPPD than in standard PD patients. It is probable that this is due to a good mixture of food with gastric, bile, and pancreatic juice. Gradual duodenal and jejunal acidification releases CCK[23] *via* gastric acid production, which is reported to be normal in PPPD patients (unpublished data). Further evidence that acid might be involved is that secretin levels increase after a meal in the PPPD (data not shown); this is important because, to our knowledge, the only known physiologic stimulus for secretin release is duodenal acidification.

However, even after standard PD, CCK was released well postprandially and no significant difference was found in the integrated CCK between control, PPPD, and standard PD.

In a previous study, we compared CCK release between two types of anastomosis of remnant alimentary tract after anterectomized PD.[24] The plasma CCK response to an oral fatty meal was significantly greater in patients who had a PD with Billroth-I type reconstruction as compared to patients with the Billroth-II type, suggesting that Billroth-I type of reconstruction is a more physiologic reconstruction for the remnant alimentary tract. In this study the patients had Billroth-I type reconstructions both in PPPD and standard PD group.

Patti[25] showed normal gastric emptying of radiolabeled solid food after PPPD using a scintillation camera. We

used a double-isotope technique to see the bile and food mixing at the same time and found complete and gradual mixing of bile and food after both standard PD and PPPD.

Our results indicate that postprandial plasma gastrin response in PPPD patients, but not PD patients, resembled that of control. In addition preserving the pylorus and the duodenal bulb as well as Billroth-I type of anastomosis between the bulb and the fourth portion of the duodenum allowed gradual transportation of food and mixture with digestive juice that enhanced CCK release before and after the meal. Gastrin and CCK release in PPPD patients may have a beneficial effect on the injured pancreas in time.

Acknowledgments

The authors thank Otsuka Assay Laboratory, who supported the gastrin and CCK assay; Professor Phillip L. Rayford, of the University of Arkansas for Medical Sciences, Little Rock, AR; Dr. Robert D. Skinner and Michael Webber for their many suggestions in preparing the manuscript; and Mae Agnew for typing the manuscript.

References

1. Barrowman JA. The trophic action of gastro-intestinal hormones. Digestion 1975; 12:92–104.
2. Petersen H, Solomon T, Grossman MI. Effect of chronic pentagastrin, cholecystokinin and secretin on pancreas of rats. Am J Physiol 1978; E286–E293.
3. Debas HT, Grossman MI. Pure cholecystokinin: pancreatic protein and bicarbonate response. Digestion 1973; 9:469–481.
4. Konturek SJ, Tasler J, Bilski J, et al. Physiological role and localization of cholecystokinin release in dogs. Am J Physiol 1986; 250:G391–G397.
5. Johnson LR. Effects of gastrointestinal hormones on pancreatic growth. Cancer 1981; 47:1640–1645.
6. Traverso LW, Longmire WP. Preservation of the pylorus in pancreaticoduodenectomy. Ann Surg 1980; 192:306–310.
7. Suzuki T, Imamura M, Kajiwara T, et al. A new method of reconstruction after pylorus-preserving pancreatoduodenectomy. World J Surg 1988; 12:645–650.
8. Pearlman NW, Stiegmann GV, Ahnen DJ, et al. Acid and gastrin levels following pyloric-preserving pancreaticoduodenectomy. Arch Surg 1986; 121:661–664.
9. Kim HC, Suzuki T, Kajiwara T, et al. Exocrine and endocrine stomach after gastrobulbar preserving pancreatoduodenectomy. Ann Surg 1987; 206:717–727.
10. Itani KMF, Coleman RE, Akwari OE, Meyers WC. Pylorus-preserving pancreatoduodenectomy. A clinical and physiologic appraisal. Ann Surg 1986; 204:655–664.
11. Grant CS, Heerden JA. Anastomotic ulceration following subtotal and total pancreatectomy. Ann Surg 1979; 190:1–5.
12. Hasimura E, Shimizu F, Nishino T, et al. Production of rabbit antibody specific for amino-terminal residues of cholecystokinin octapeptide (CCK-8) by selective suppression of cross-reactive antibody response. J Immunol Methods 1982; 55:375–387.
13. Kanayama S, Himeno S, Kurokawa M, et al. Marked prolongation in disappearance half-time of plasma cholecystokinin-octapeptide in patients with hepatic cirrhosis. Am J Gastroenterol 1985; 80: 557–560.
14. Sato T, Imamura M, Matsuro S, et al. Gastric acid secretion and gut hormone release in patients undergoing pancreaticoduodenectomy. Surgery 1986; 99:728–734.
15. Johnson AG, McDermott SJ. Sensitive bioassay of cholecystokinin in human serum. Lancet 1973; ii:589–591.
16. Lorusso D, Misciagna G, Noviello MR, Tarantino S. Cholelithiasis after Billroth-II gastric resection. Surgery 1988; 103:579–583.
17. Satake K, Takeuchi T, Watanabe S, Nishiwaki H. Postprandial plasma cholecystokinin response in patients after gastrectomy and pancreatoduodenectomy. Am J Gastroenterol 1986; 81:1038–1042.
18. Hopman WPM, Jansen JBMJ, Lamers CHHW. Plasma cholecystokinin response to oral fat in patients with Billroth-I and Billroth-II gastrectomy. Ann Surg 1984; 199:276–280.
19. Becker HD, Werner M, Schafmayer A. Release of radioimmunologic cholecystokinin in human subject. Am J Surg 1984; 147:124–128.
20. Guzman S, Chayvialle JA, Banks WA, et al. Effect of vagal stimulation on pancreatic secretion and on blood levels of gastrin, cholecystokinin, secretin, vasoactive intestinal peptide, and somatostatin. Surgery 1979; 86:329–336.
21. Fried GM, Ogden WD, Sakamoto T, et al. Experimental evidence for a vagally mediated and cholecystokinin-independent enteropancreatic reflex. Ann Surg 1985; 202:69–74.
22. Ogden WD, Fried GM, Sakamoto T, et al. Distribution of cholecystokinin in the alimentary tract of dogs. Surg Forum 1982; 33: 132–134.
23. Chen YF, Chey WY, Chang TM, Lee KY. Duodenal acidification releases cholecystokinin. Am J Physiol 1985; 249:G29–G33.
24. Inoue K, Tobe T, Suzuki T, et al. Plasma cholecystokinin and pancreatic polypeptide response after radical pancreatoduodenectomy with Billroth-I and Billroth-II type of reconstruction. Ann Surg 1987; 206:148–154.
25. Patti MG, Pellegrini CA, Way LW. Gastric emptying and small bowel transit of solid food after pylorus-preserving pancreaticoduodenectomy. Arch Surg 1987; 122:528–532.