Plasma cholecystokinin levels and gallbladder volumes after proctocolectomy with ileal pouch–anal anastomosis

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Background. *The colon and rectum contain regulatory peptides in mucosal endocrine cells, which suggests a hormonal role. In animal studies colectomy leads to increased plasma levels of cholecystokinin. Little is known about the effects of proctocolectomy with ileal pouch–anal anastomosis on the release of cholecystokinin in human beings. Therefore we studied the effects of this procedure on fasting, postprandial, and bombesin-stimulated plasma cholecystokinin levels and gallbladder volumes.*

Methods. *Ten patients who had undergone protocolectomy with ileal pouch–anal anastomosis and 12 healthy volunteers participated in the study. Fasting and postprandial plasma cholecystokinin levels and gallbladder volumes were studied for 3 hours at 15-minute intervals. In a second experiment plasma cholecystokinin levels were measured before and during intravenous administration of bombesin in six patients with ileal pouch and five healthy volunteers.*

Results. *Fasting plasma cholecystokinin levels were higher ($p < 0.05$) in patients with ileal pouch–anal anastomosis (2.6 ± 0.3 pmol/L) compared with controls (1.7 ± 0.2 pmol/L). Integrated postprandial plasma cholecystokinin levels were also distinctly higher ($p < 0.01$) in patients (978 ± 126 pmol/L · 180 min) than in controls (588 ± 60 pmol/L · 180 min). Mean fasting gallbladder volume was significantly ($p < 0.01$) decreased in patients with ileal pouch–anal anastomosis (18 ± 2 ml) compared with controls (28 ± 2 ml). Postprandial gallbladder emptying as measured by percentage change was similar in both groups. After infusion of bombesin, integrated plasma cholecystokinin responses were higher ($p < 0.05$) in patients (161 ± 20 pmol/L · 20 min) than in controls (90 ± 12 pmol/L · 20 min).*

Conclusions. *Fasting, postprandial, and bombesin-stimulated plasma cholecystokinin levels are elevated in patients with ileal pouch–anal anastomosis compared with controls. Fasting gallbladder volume is decreased after ileal pouch–anal anastomosis. These findings suggest that the colon contains a factor that inhibits the release of cholecystokinin. (SURGERY 1995;117:705-11.)*

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PROCTOCOLECTOMY WITH ileal pouch–anal anastomosis (IPAA) is an attractive and widely accepted alternative to permanent ileostomy in patients operated on for severe ulcerative colitis or familial polyposis coli, because the normal route of defecation is preserved.[1, 2] Long-term functional results are generally gratifying because defecation frequency and degree of incontinence are acceptable in most patients.[3-7]

The colon and rectum contain regulatory peptides in mucosal endocrine cells, which suggests a hormonal role.[8] Harper et al.[9, 10] demonstrated that extracts from colonic and ileal mucosa of cats and pigs markedly inhibited both pancreatic protein secretion and gallbladder contraction. Intraluminal perfusion of the colon with nutrients induces endocrine effects.[11-16] Perfusion of the colon with oleic acid inhibits the release of cholecystokinin and pancreatic enzyme secretion in dogs.[15] Moreover, it has been shown that subtotal colectomy results in an increased postprandial cholecystokinin release in rats and dogs.[17, 18] These findings suggest that the colon contains a factor that suppresses the release of cholecystokinin. Little is known, however, about the effects of proctocolectomy on gastrointestinal physiology and circulating gut hormone responses in human beings.

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The aim of this study was to examine the effect of proctocolectomy with IPAA on the release of cholecystokinin and gallbladder motility in human beings. Therefore we have studied fasting and postprandial plasma cholecystokinin levels and gallbladder volumes (GBVs) in these patients. The results were compared with those obtained in healthy volunteers. To study the release of cholecystokinin independently of a meal, we further have studied cholecystokinin secretion during intravenous administration of bombesin, a neuropeptide that potently stimulates the release of cholecystokinin.[19-21]

METHODS

Subjects. Twelve healthy subjects (seven male and five female) and 10 patients who had undergone proctocolectomy with IPAA (three male and seven female; three cases of familial polyposis coli and seven cases of ulcerative colitis) were studied. In all patients a J pouch had been constructed 6 months to 7 years (median, 4 years) before this study was performed. The diverting loop ileostomy had been closed in all. None of the patients with IPAA had experienced pouchitis. Mean age, weight, length, and body mass index (BMI) were similar in both groups (Table). None of the healthy subjects had a history of previous abdominal operation or gastrointestinal disease, and none of the patients with IPAA had undergone cholecystectomy. Fasting plasma cholecystokinin levels were determined in an additional five patients with IPAA and three healthy volunteers (both groups, total 15 subjects). To assess whether postprandial plasma cholecystokinin levels change with time of follow-up, the correlation between the integrated postprandial plasma cholecystokinin levels and the length of time after operation was calculated. Informed consent was obtained from each subject, and the protocol was approved by the Ethics Committee of the Nijmegen University Hospital.

Experimental protocol. All subjects reported at 8:30 AM at the gastrointestinal research laboratory after an overnight fast. The subjects ingested a standardized breakfast (at t = 0 minutes) composed of one slice of bread, 5 gm butter, 20 gm cheese, one boiled egg, 150 ml yogurt, and one cup of tea with 5 gm sugar (21 gm protein, 21.5 gm fat, 34 gm carbohydrate). Venous blood samples for analysis of plasma cholecystokinin levels were drawn before (at t = [<]0m;−5 and 0 minutes) and at 15-minute intervals from 0 to 120 minutes and at 30-minute intervals from 120 to 180 minutes after the meal through an indwelling catheter placed in an antecubital vein. Blood was collected into glass tubes containing ethylenediamine tetraacetic acid. After centrifugation the separated plasma was frozen at −20° C until analysis. GBVs were measured at the same time points.

In a second experiment the response of plasma cholecystokinin to intravenous administration of bombesin (5 ng/kg/min) was measured in six patients with IPAA (two male and four female; mean age, 34 years; range, 23 to 41 years) and five healthy volunteers (three male and two female; mean age, 47 years; range, 43 to 53 years) after an overnight fast. Three of the six patients with IPAA had also participated in the first experiment. None of the patients with IPAA had experienced episodes with pouchitis. None of the healthy volunteers in the bombesin experiment had participated in the first experiment. Bombesin was administered through an indwelling catheter in an antecubital vein. Blood samples for determination of plasma cholecystokinin levels were drawn from a catheter in an antecubital vein in the opposite arm before and at 5-minute intervals for 20 minutes during bombesin infusion.

Gallbladder emptying. GBV was measured by means of real-time ultrasonography with the sum of cylinders method by using a computerized method.[22] In this method the longitudinal scan of the gallbladder is divided into a series of cylinders of equal height, with diameters perpendicular to the longitudinal axis of the gallbladder image. The uncorrected volume is the sum of volumes of these separate cylinders. To correct for the displacement of the longitudinal image of the gallbladder from the central axis, a correction factor is calculated from the longitudinal and transverse scans of the gallbladder. GBV is calculated by multiplication of the uncorrected volume with the square of the correction factor. Two longitudinal and two transverse images of the gallbladder were obtained at each time point. The mean of two measurements was used for further analysis. The variation of GBV measurements by using this method ranges from 6.2% to 10.0%. Gallbladder emptying and percentage gallbladder emptying were calculated by using the following formulas:

$$\text{Maximum gallbladder emptying} = GBV_0 - GBV_{min}$$

$$\text{Percentage gallbladder emptying} = 100\% \cdot (GBV_0 - GBV_{min})/GBV_0$$

where GBV_0 is mean fasting GBV (average of GBV at t = −5 and 0 minutes) and GBV_{min} is smallest postprandial GBV.

Plasma cholecystokinin levels. Cholecystokinin was measured in plasma by a sensitive and specific radioimmunoassay.[23, 24] The antibody used (T204) was raised in rabbit after the fourth immunization with albumin-coupled crude porcine cholecystokinin and used in a final dilution of 1:80,000. The antibody binds to all carboxy-terminal cholecystokinin peptides containing the sulfated tyrosyl region. The antibody shows less than 2% cross-reactivity with sulfated gastrins and does not bind to unsulfated forms of gastrin or structurally unrelated peptides, like insulin, secretin, pancreatic polypeptide,

bombesin, and neurotensin. Synthetic human cholecystokinin$_{33}$ coupled to ^{125}I-hydroxyphenylpropionic acid succinimide ester (Bolton-Hunter reagent) was used as label and as standard preparation. The detection limit of this assay is 0.5 pmol/L. The intraassay variation ranges from 4.6% to 11.5% and the interassay variation from 11.3% to 26.1%.

Statistical analysis. Results were expressed as mean ± SEM. Fasting plasma cholecystokinin levels and fasting GBVs were calculated as the mean of two basal measurements (−5 and 0 minutes). Integrated plasma cholecystokinin secretion in response to the meal or to bombesin infusion was determined by calculating the area under the plasma concentration versus time curve by using the trapezoidal rule. Statistical analysis was performed with Student's *t* test for unpaired results or the rank sum test when appropriate. A two-tailed p value of less than 0.05 was considered statistically significant. The correlation between integrated postprandial plasma cholecystokinin levels and length of postoperative time of follow-up was calculated with the Pearson correlation coefficient.

RESULTS

Fasting and postprandial plasma cholecystokinin levels. Fasting plasma cholecystokinin levels were significantly higher ($p < 0.05$) in patients with IPAA (2.6 ± 0.3 pmol/L) compared with the healthy controls (1.7 ± 0.2 pmol/L). Postprandial plasma cholecystokinin levels increased rapidly and significantly in both groups. In healthy volunteers the mean peak plasma cholecystokinin level was 4.2 ± 0.5 pmol/L and in patients with IPAA 7.8 ± 1.1 pmol/L ($p = 0.003$). The mean time to peak plasma cholecystokinin levels was similar in both groups, 58 ± 12 minutes in healthy controls and 50 ± 11 minutes in patients with IPAA. Plasma cholecystokinin concentration versus time curves are shown in Fig. 1. Integrated postprandial plasma cholecystokinin levels were significantly higher ($p < 0.01$) in the patients with IPAA (797 ± 77 pmol/L · 180 min) compared with the healthy controls (516 ± 57 pmol/L · 180 min). Individual integrated postprandial plasma cholecystokinin levels are shown in Fig. 2. The Pearson correlation coefficient between integrated postprandial plasma cholecystokinin levels and time of postoperative follow-up was −0.63 ($p = 0.052$).

Fasting GBVs and postprandial gallbladder emptying. Fasting GBVs were significantly smaller ($p < 0.01$) in patients with IPAA (18 ± 2 ml) when compared with healthy controls (27 ± 2 ml). Individual fasting GBVs are shown in Fig. 3. Mean fasting and postprandial GBVs are depicted in Fig. 4. Maximum gallbladder emptying was 23 ± 2 ml in controls and 15 ± 3 ml in patients with IPAA ($p < 0.01$). The smallest GBVs were reached at 95 ± 13 minutes in patients with IPAA (3 ± 1 ml) and at 81 ± 7 minutes (not significant) in controls (5 ± 1 ml, not significant). The percentage gallbladder emptying was similar in both groups (controls, 82% ± 3%; patients with IPAA, 81% ± 4%, not significant). No correlation was observed between fasting GBV and time of postoperative follow-up.

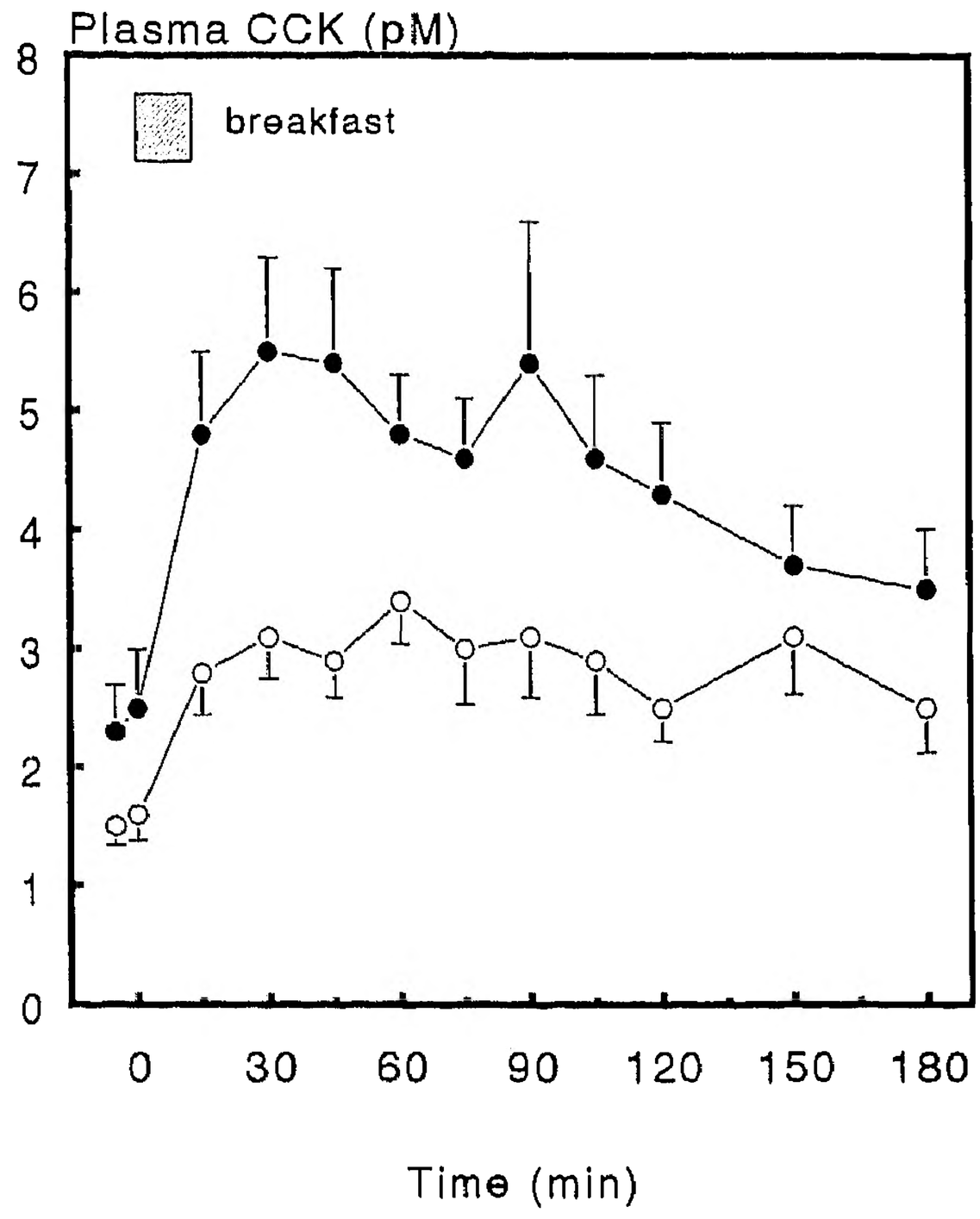

Fig. 1. Fasting and postprandial plasma cholecystokinin *(CCK)* levels versus time curves (mean ± SEM) in controls *(open markers)* and patients with IPAA *(closed markers)*.

Plasma cholecystokinin responses to bombesin-infusion. Basal plasma cholecystokinin levels were similar in both groups (controls, 1.8 ± 0.3 pmol/L; patients with IPAA, 1.8 ± 0.4 pmol/L). During infusion of bombesin the integrated plasma cholecystokinin response was significantly higher ($p < 0.05$) in patients with IPAA (161 ± 20 pmol/L · 20 min) compared with controls (90 ± 12 pmol/L · 20 min). Fig. 5 shows the mean plasma cholecystokinin time curves in five healthy controls and six patients with IPAA before and during infusion of bombesin.

DISCUSSION

In the present study we have demonstrated that postprandial and bombesin-stimulated plasma cholecystokinin levels are increased after proctocolectomy with IPAA. To our knowledge this is the first time that the effect of proctocolectomy on plasma cholecystokinin levels and GBVs has been studied in human beings.

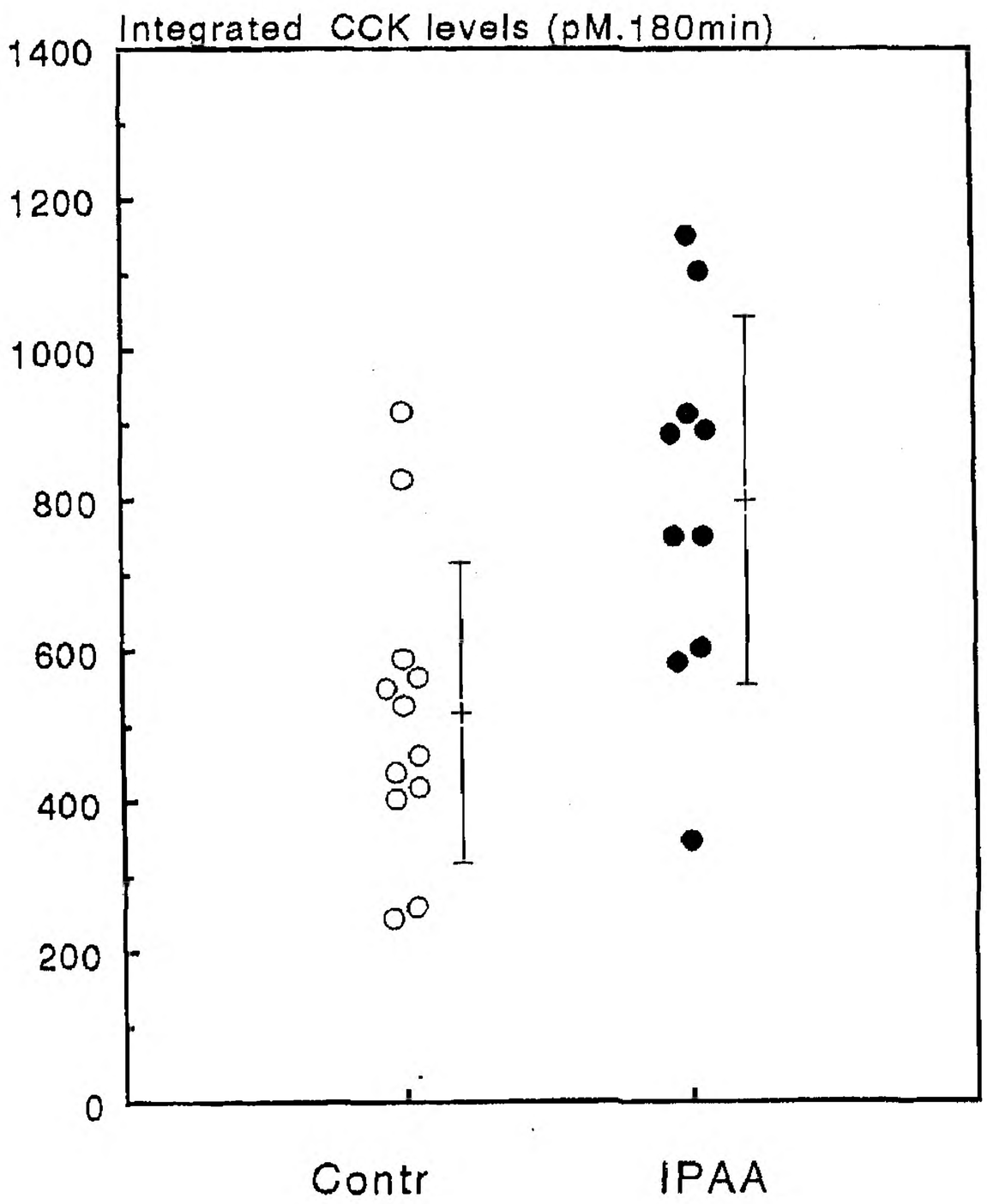

Fig. 2. Individual integrated postprandial plasma cholecystokinin *(CCK)* levels in healthy controls *(open markers)* and patients with IPAA *(closed markers)*. Integrated postprandial cholecystokinin levels were significantly higher in patients with IPAA ($p < 0.01$). *Error bars* indicate standard deviation.

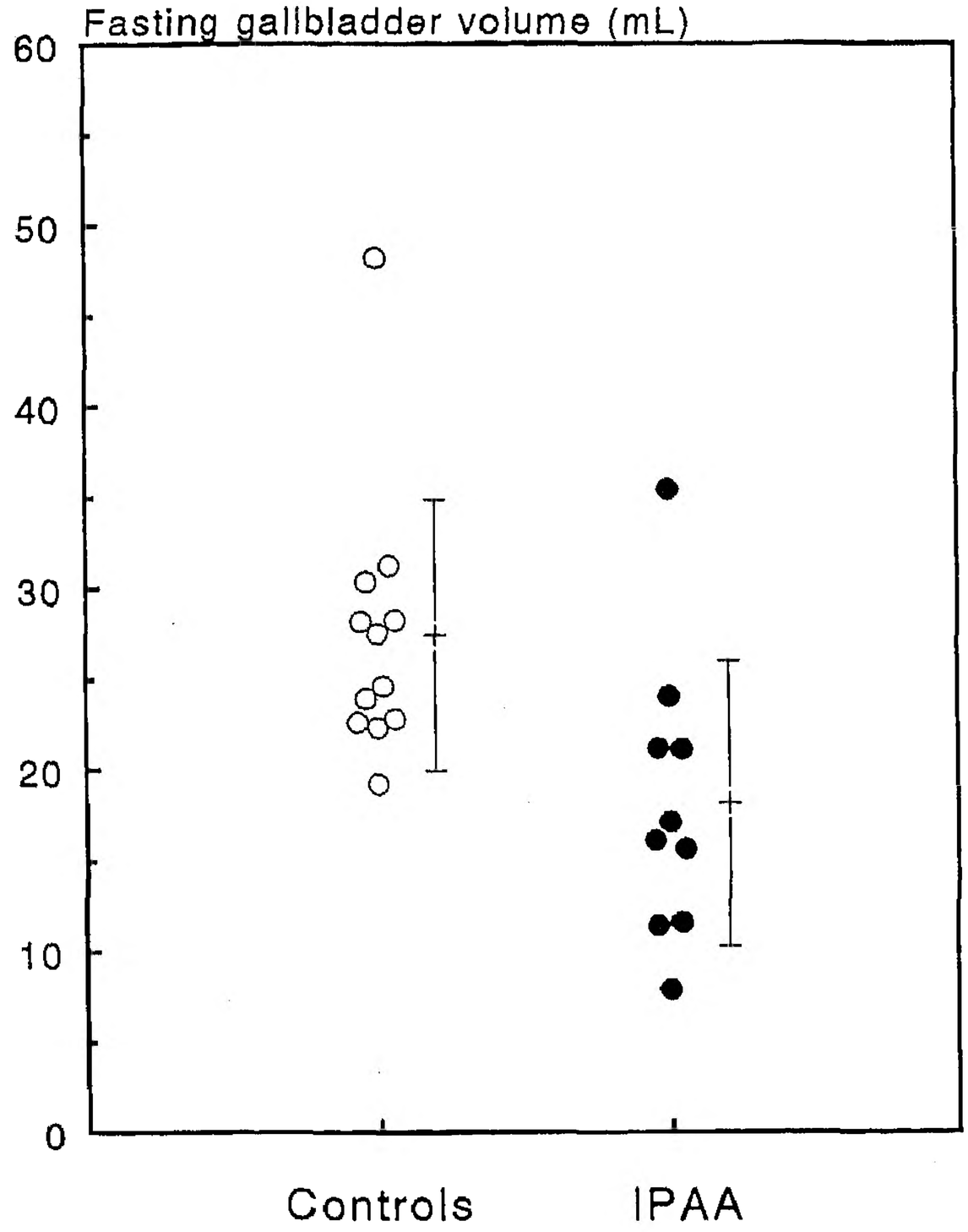

Fig. 3. Individual fasting GBVs in healthy controls *(open markers)* and patients with IPAA *(closed markers)*. *Error bars* indicate standard deviation. Mean fasting GBV in healthy controls (28 ± 2 ml) was significantly higher compared with patients with IPAA (18 ± 2 ml, $p < 0.01$).

Table. Gender, mean age, weight, height, and BMI of patients with IPAA and healthy volunteers (controls)

	Controls	*Patients with IPAA*	*p Value*
Gender	7 M, 5 F	7 M, 3 F	0.67
Age (yr, range)	36.3 (22-61)	35.7 (22-49)	0.70
Weight (kg)	77 ± 3	77 ± 3	0.99
Height (m)	1.77 ± 0.03	1.75 ± 0.03	0.78
BMI (kg/m^2)	24.9 ± 0.9	25.2 ± 0.9	0.80

No significant differences in these parameters between controls and patients with IPAA were observed.

Probably as a result of fasting hypercholecystokinemia, fasting GBVs are decreased in patients with IPAA. Basal plasma cholecystokinin levels were slightly but significantly elevated after proctocolectomy compared with the healthy controls in our meal study. However, in the bombesin study plasma cholecystokinin levels were similar in both groups. This apparent discrepancy is likely to be due to the small number of subjects in the bombesin experiment compared with the meal study. Therefore the power to detect a true difference in basal plasma cholecystokinin levels may have been too low in the bombesin experiment (type II error).

Previously it has been shown that subtotal colectomy results in an increased postprandial plasma cholecystokinin release in rats and dogs.[17, 18] Pancreatic weight, digestive enzyme concentration, and secretion capacity increase after large bowel resection in rats.[25] These effects are supposed to be induced by elevated plasma cholecystokinin levels.

Several mechanisms may account for the increased cholecystokinin levels after proctocolectomy. First, a negative feedback mechanism on the release of cholecystokinin exerted by an unknown inhibiting colonic factor may be eliminated after proctocolectomy. This hypothesis is supported by the finding that perfusion of the colon with oleic acid has been shown to inhibit pancreatic protein secretion in dogs,[12] cats,[13] and human beings.[14, 15] Inoue et al.[16] have demonstrated that this inhibition of pancreatic exocrine protein secretion in dogs is due, at least in part, to suppression of cholecystokinin release. Under normal conditions, however, nutrients like oleic acid do not enter the colon in concentrations used in these perfusion experiments. Therefore it is unclear whether these nutrients play a functional

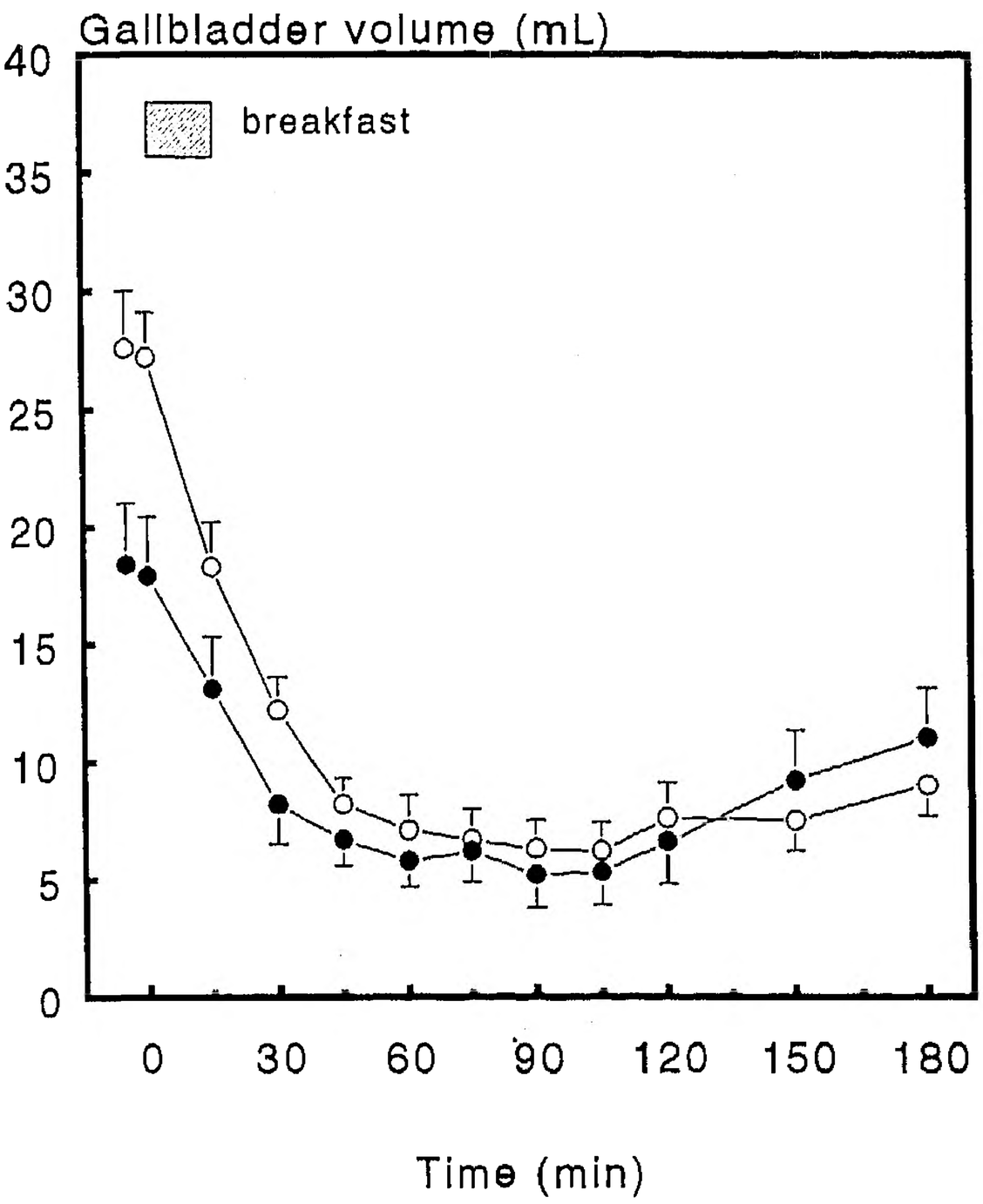

Fig. 4. Mean (±SEM) fasting and postprandial GBVs in healthy controls *(open markers)* and patients with IPAA *(closed markers)*. Postprandial gallbladder emptying as measured by percentage change was similar in both groups.

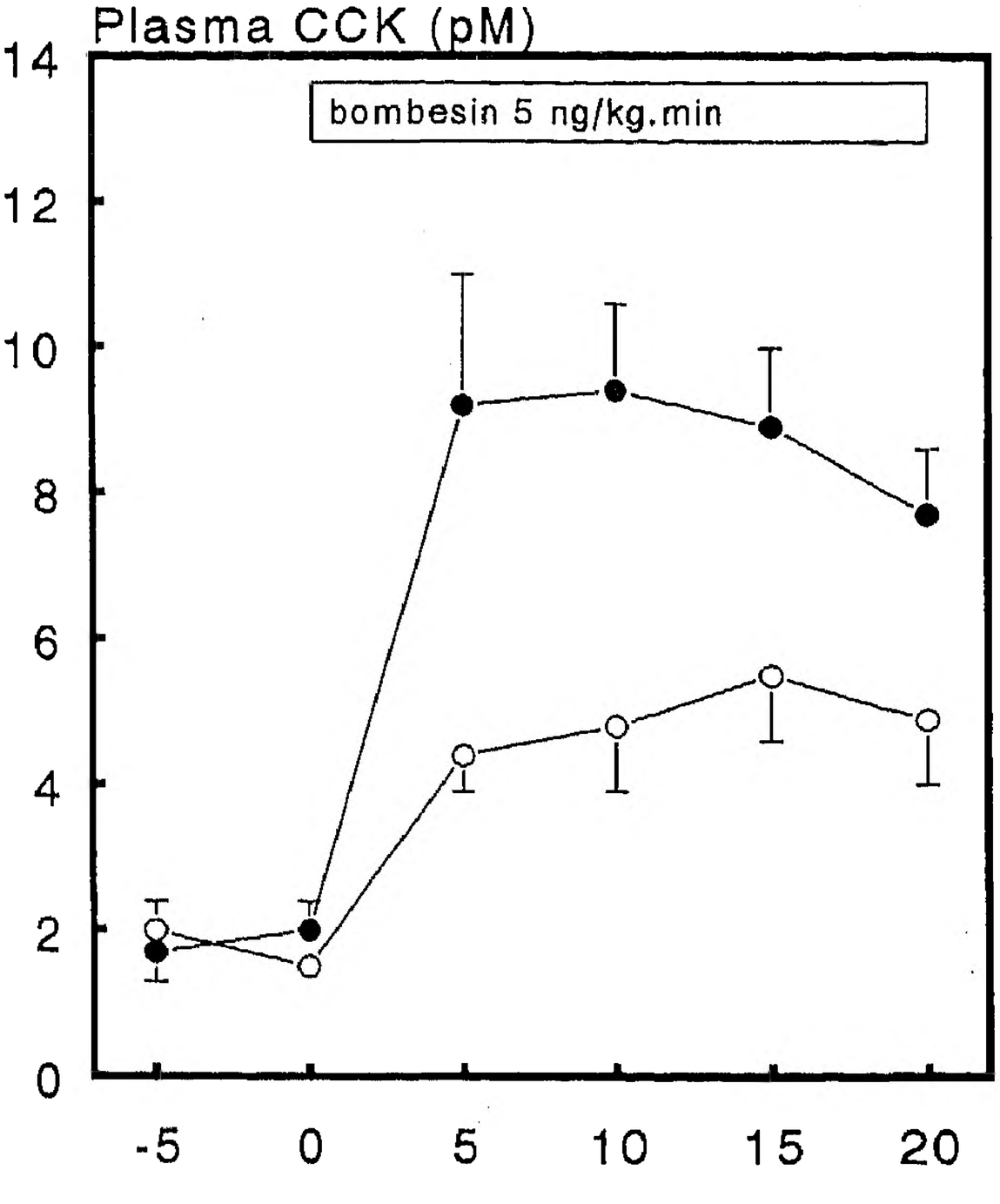

Fig. 5. Plasma cholecystokinin *(CCK)* response (mean ± SEM) to infusion of bombesin in five healthy controls *(open markers)* and six patients with IPAA *(closed markers)*. Integrated cholecystokinin response to bombesin infusion was significantly higher in patients with IPAA ($p < 0.05$).

role in a feedback control of proximal cholecystokinin release in healthy human beings.

Lluis et al.[26] have shown that a substance released from the colon inhibits pancreatic secretion by inhibiting cholecystokinin release in dogs. This substance, peptide YY (PYY), has been found primarily in mucosal endocrine cells in the ileum, colon, and rectum of several species[27-29] including human beings.[30] Therefore proctocolectomy may lead to lower circulating PYY levels and hence to elevated plasma cholecystokinin levels in human beings. Indeed, fasting PYY levels have been found to be decreased in patients who had undergone total colectomy[31] or colonic resection with ileostomy.[32] This topic, however, remains controversial because Armstrong et al.[33] have found increased fasting and postprandial plasma PYY levels and increased tissue levels of PYY 1 year after proctocolectomy with IPAA in dogs. It was suggested that an increased synthesis and release of PYY are an adaptive process that may contribute to functional improvement by slowing small intestine transit. This suggestion is supported by studies of Pietroletti et al.,[34] who found elevated fasting and postprandial PYY levels after proctocolectomy with IPAA in human beings. Although not of enough statistical power ($p = 0.052$), we found a trend toward declining cholecystokinin levels with time after operation, probably as a result of adaptation. It could be speculated that during follow-up after proctocolectomy PYY synthesis in the terminal ileum and circulating PYY levels gradually increase as a result of adaptation. Assuming a suppressive effect of PYY on the release of cholecystokinin, plasma cholecystokinin levels may initially increase after proctocolectomy and gradually decline during follow-up.

Previous studies have shown that ileal perfusion of fat emulsions markedly inhibits gastric emptying, small bowel transit, and jejunal motor activity.[35-37] This "ileal brake" correlates well to increased plasma levels of PYY.[37] Intravenous infusion of PYY at physiologic levels slows the mouth to cecum intestinal transit and the rate of gastric emptying.[38, 39] These data suggest that the ileal brake may be mediated in part by PYY. Small intestine transit is also slowed in patients with IPAA.[40] It could be speculated that elevated PYY levels mediate this inhibition of small intestine transit. Removal of the colon does not eliminate the ileal brake because it has been shown that oleic acid infusion into the ileal pouch slows gastric emptying and small intestine transit and

increases plasma levels of PYY.[41, 42] However, it is unclear to what extent stool frequency is influenced by the ileal brake mechanism after proctocolectomy with IPAA. As a result of inflammation of the ileal mucosa, the production of PYY might be decreased in patients with pouchitis. This might contribute to rapid small intestine transit and increased stool frequency in these patients.

Further studies are needed to evaluate the role of PYY in the adaptive response during follow-up after proctocolectomy with IPAA and the relationship between plasma levels of PYY and cholecystokinin, in patients both with and without pouchitis. Withdrawal of unknown colonic factors with a possible inhibitory effect on the release of cholecystokinin may also induce hypercholecystokinemia after proctocolectomy.

Previously we have reported that postprandial conjugated serum bile acid levels are decreased in patients with IPAA compared with healthy subjects with an intact colon.[43] An increased fecal excretion of bile acids has been observed in patients with a Kock continent ileostomy[44-46] and in patients with IPAA.[47, 48] Probably bile acids are reabsorbed less effectively by the ileal pouch mucosa in comparison with the mucosa of the normal terminal ileum. The bile acid pool and the bile acid output into the duodenum decrease if fecal losses are substantial. Because the release of cholecystokinin is inhibited by bile acids in the duodenal lumen,[49, 50] elevated plasma cholecystokinin concentrations after proctocolectomy may also be due to a decreased load of bile acids in the proximal part of the small intestine.

In conclusion, basal, postprandial, and bombesin-stimulated plasma cholecystokinin levels are elevated after proctocolectomy with ileal pouch–anal anastomosis in human beings. Probably as a result, fasting GBVs are decreased after proctocolectomy. The mechanisms responsible for hypercholecystokinemia in patients with IPAA are still incompletely understood and need further investigation.

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