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Altered Postprandial Motility in Chronic Pancreatitis: Role of Malabsorption

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Background & Aims: Intraileal nutrients modulate gastrointestinal motility, but effects of maldigestion on postprandial motility are unknown. The aim of this study was to compare motor responses with ileal nutrient exposure in health and pancreatic insufficiency after a meal or intraluminal perfusion. **Methods:** After oroileal multilumen intubation for duodeno-jejuno-ileal sampling, marker perfusion, and motility recording, 14 normal subjects and 12 patients with severe pancreatic insufficiency received a labeled liquid meal twice, either with placebo or pancreatin. Effects of intraileal nutrient perfusion on fed motility induced by duodenal amino acid perfusion were also investigated. **Results:** Compared with normals, untreated patients had greater cumulative ileal nutrient delivery (69 ± 21 vs. 487 ± 232 kJ), shorter fed pattern (196 ± 22 vs. 131 ± 14 minutes), greater 90% gastric emptying (163 ± 12 vs. 128 ± 10 minutes), and faster small intestinal transit (86 ± 9 vs. 44 ± 6 minutes). Pancreatin reversed these changes. Ileal nutrient perfusion converted fed into interdigestive-like motility in normals (7 of 8) and patients (4 of 5). **Conclusions:** In subjects with pancreatic insufficiency, a low-energy liquid meal induces shorter fed motor pattern associated with accelerated gastric emptying and intestinal transit compared with healthy subjects. Because changes responded to enzyme treatment and could be reproduced by ileal nutrient perfusion, ileal delivery of malabsorbed chyme may be involved as a mechanism.

Under physiological conditions, gastrointestinal motility and exocrine pancreatic secretion are regulated in concert,¹⁻³ but only a few studies have addressed the question of whether postprandial motility is altered when pancreatic function is disturbed. In chronic pancreatitis, contradictory results have been reported for gastric motility,⁴⁻⁷ and intestinal motility has not been studied. However, because nutrient exposure of the small intestinal lumen is a major regulatory factor controlling gastrointestinal motor functions, it is conceivable that postprandial motility is affected in states of increased

quantities of unabsorbed nutrient delivered to proximal and distal small intestinal sites as expected in untreated severe exocrine pancreatic insufficiency.⁸ This concept is supported by several studies showing that increased nutrient loads delivered to the distal intestine modulate human intestinal motility.⁹⁻¹²

Consequently, we reasoned that motor regulation in the late-postprandial period may be altered in severe exocrine pancreatic insufficiency. To test this hypothesis, we used two different experimental protocols.

In protocol 1, we compared postprandial motor responses after a standardized low-energy liquid test meal among normal subjects and patients with untreated pancreatic insufficiency and correlated them with nutrient delivery rates within the proximal and distal small intestinal lumen. These experiments were repeated in the same subjects to determine the effects of pancreatic enzyme supplementation.

In protocol 2, we compared the effects of intraileal perfusion of nutrient with those of saline (as volume control) on fed motility both in normal individuals and patients with chronic pancreatitis, using the same subjects as their own controls. Duodenal and ileal nutrient loads were chosen to be of similar magnitude as those measured in protocol 1 during the third postprandial hour in untreated pancreatic insufficiency.

Materials and Methods

Patients and Normal Subjects

The protocol was approved by the Institutional Ethical Committee. After giving informed written consent, 22 healthy subjects (15 men and 7 women; age range, 22-46 years) and 12 patients with chronic pancreatic insufficiency (9 men and 3 women; age range, 34-59 years) participated in the study. All healthy subjects had a normal history and no abnormalities on physical examination.

Abbreviations used in this paper: GLP-1, glucagon-like peptide 1; PSP, phenolsulfonphthalein.

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Table 1. Clinical Characteristics of the Patients With Chronic Pancreatitis and Severe Exocrine Pancreatic Insufficiency

Patient no.	Sex	Age (yr)	Etiology	Duration of CP (yr)	Fecal fat (g/24 h)	SC test (% normal)	Diabetes mellitus
1	M	47	Alcoholic	10	35	0.7	-
2 ^a	M	44	Alcoholic	6	42	1.8	-
3	F	55	Idiopathic	7	26	3.8	-
4	M	47	Alcoholic	9	52	0.7	-
5 ^a	F	46	Alcoholic	8	26	4.2	-
6 ^a	M	48	Alcoholic	11	30	1.2	-
7 ^a	M	34	Alcoholic	6	29	3.8	-
8	M	59	Alcoholic	16	34	0.6	+
9	F	49	Alcoholic	12	40	2.0	-
10	M	43	Alcoholic	8	32	1.2	-
11	M	39	Idiopathic	18	28	1.6	+
12 ^a	M	52	Alcoholic	7	78	0.2	-

CP, chronic pancreatitis; SC test, secretin-erulein test.

^aPatient participated in both experimental protocols.

All patients had had symptomatic chronic pancreatitis for 9.8 ± 1.7 years (range, 6–18 years) and were seen in our institution at regular intervals. Diagnosis of chronic pancreatitis had been established by a typical clinical history and characteristic abnormalities in abdominal ultrasonography, computerized tomography, and endoscopic retrograde cholangiopancreatography in all patients. At the time of the study, each patient had severe exocrine pancreatic insufficiency established by direct pancreatic function test within 12 months of the study (secretin-erulein test: mean trypsin output, $1.8\% \pm 0.4\%$ of normal mean output) and manifest steatorrhea (fecal fat excretion without enzyme supplementation: range, 26–78 g/day). All patients had been free of acute symptomatic attacks of pancreatitis or severe pain for at least 2 years. Pancreatic enzyme supplementation and any medication with (potential) effects on gastrointestinal motility were discontinued 7 days before each study. Chronic pancreatitis was of alcoholic etiology in 10 patients, all of whom had discontinued alcohol abuse several years ago, and was idiopathic in 2 patients. Two patients had diabetes mellitus controlled by insulin for 2 and 4 years, respectively, and were administered 12 and 16 IU, respectively, of human insulin with their test meal. No patient had evidence of autonomic or somatic neuropathy or other major extrapancreatic alcoholic or diabetic complications, and there was no history of additional gastrointestinal or other relevant disorders. Important clinical features of these patients are presented in Table 1. Five of the patients (patients 2, 5–7, and 12) participated in both experimental protocols.

Gastrointestinal Intubation, Motility Recording, and Sampling

Subjects were fasted overnight and then intubated at 6 AM with a polyvinyl multilumen oroileal tube (largest OD, 7.2 mm) that was placed with its tip in the distal ileum (240 cm from the mouth). In this position, the aspiration ports (ID, 2.0 mm) were in the ascending duodenum just proximal to the ligament of Treitz, in the midjejunum (90 cm from the pylorus), and in the terminal ileum (150 cm from the pylorus).

Perfusion ports (ID, 1.0 mm) for the dilution marker polyethylene glycol (45 mg/min) were at the papilla of Vater; for intraluminal solutions (described below), they were in the distal ileum (25 cm from the tip of the tube). Seven integrated catheters (ID, 0.8 mm) were perfused with deionized water and served as pressure recording ports; three were located in the distal antrum (spaced 5 cm apart) and four in the small intestine (10, 25, 40, and 55 cm distally from the pylorus). Correct tube position was reached usually after 3–5 hours and was verified by brief fluoroscopy before the start and after the end of each study. After tube placement, continuous duodenal polyethylene glycol perfusion and recording of intestinal motility was begun.

Each perfusion catheter was connected to a low-compliance perfusion system¹³; the voltage output of each calibrated pressure transducer was preamplified and recorded by an eight-channel recorder (Sensormedics, Essen, Germany).

From each aspiration site, 2–3-mL aliquots of intraluminal contents were aspirated by hand during every 15-minute period throughout the study and collected into vials that were immersed in ice. To ensure rapid collection of fresh intraluminal samples, the tube to each site was flushed with a volume of air equal to its dead space (duodenal, 3 mL; jejunal, 4 mL; and ileal, 5 mL) immediately before and after the intestinal juice was aspirated. Samples were analyzed on the same day or within 2 days of the study. Blood samples were collected at 30-minute intervals.

Experimental Design

Protocol 1: correlation of postprandial motility and luminal nutrient delivery. Each participant was studied twice on separate days and, with a test meal, was administered either placebo or pancreatin in random order and double-blind fashion.

Placebo study. Normal subjects ($n = 14$) and patients with pancreatic insufficiency ($n = 12$) ingested a standard homogenized semiliquid test meal within 15 minutes; this meal was chosen to minimize intraindividual and interindivid-

ual variations in gastric emptying. The meal consisted of 41.4 g of rice starch, 10.2 g of emulsified triolein, and 11.4 g of sodium caseinate (i.e., 55%, 30%, and 15%, respectively, of total energy content of 1257 kJ; total volume, 300 mL; provided by Dr. Kessler, Fresenius, Oberursel, Germany). It contained phenolsulfonphthalein (PSP; 100 μ g/mL) as a liquid delivery marker to luminal sites; absorption of PSP by the intact gastric or intestinal mucosa is <1% per hour.¹⁴⁻¹⁸ With the meal, all participants were administered the placebo (heat-inactivated pancreatin without measurable enzymatic activity).

Pancreatin study. The same participants received an identical meal together with pancreatic enzyme supplementation (pancreatin powder: lipase, 30 kU; amylase, 24 kU; proteases, 2 kU; kindly provided by Dr. Rolle, Sanol GmbH, Monheim, Germany).

Protocol 2: effect of ileal nutrient perfusion on fed-motility pattern. In 8 fasting normal subjects and 5 of the patients with chronic pancreatitis participating in protocol 1 (Table 1), a fed intestinal motility pattern was induced by continuous duodenal perfusion (3 mL/min) with a mixture of essential amino acids (450 μ mol/min). This perfusate (rather than a mixed nutrient emulsion) was chosen because it is an established moderate endogenous stimulus of intestinal motility¹⁰ with an energy load (2.4 kJ/min) comparable to duodenal energy flow rate in the third postprandial hour in the patients with untreated pancreatic insufficiency studied in protocol 1. Its intraduodenal perfusion results in negligible delivery of unabsorbed energy into the distal intestine. After 1 hour, an additional ileal perfusion (3 mL/min) was administered for 30 minutes. Control and test perfusates were administered in random order and separated by 4 hours to avoid potential carry-over effects.

Test study. The ileal test perfusate consisted of a mixed nutrient solution (carbohydrate, 17.5 mg/mL; lipid, 4.5 mg/mL; and protein, 5.0 mg/mL), with a resulting energy perfusion rate of 1.64 kJ/min. The energy load and composition of ileal nutrient perfusion were chosen to be similar to ileal samples in untreated pancreatic insufficiency during the third postprandial hour obtained in protocol 1. The proportion of ileal nutrients in untreated patients was similar to that of the test meal, which is in contrast to normal subjects, in which protein, in particular pancreatic enzymes, represents a major component of late-postprandial ileal contents.¹⁹

Control study. Normal saline instead of nutrients was perfused intraileally as the volume control.

Chemical, Motility, and Statistical Analyses

In luminal samples, total carbohydrate concentration was measured as glucose using a commercial hexokinase-glucose-6-phosphate-dehydrogenase assay (Glucoquant; Boehringer, Mannheim, Germany) after pretreatment with amyloglucosidase (E.C.3.2.1.3; Sigma Chemical Co., St. Louis, MO) as described previously²⁰; the same glucose assay was used to measure plasma glucose. Commercial kits were used to determine luminal lipid (triglycerides plus fatty acids) concentra-

tion enzymatically (Boehringer) and protein concentration spectrophotometrically (Bio-Rad protein assay; Bio-Rad Laboratories, Munich, Germany). Luminal energy content was approximated as the sum of the carbohydrate (at 17.2 kJ/g), protein (at 17.2 kJ/g), and fat (at 38.9 kJ/g) contents in each sample (1 kJ = 0.239 kcal). Luminal pH was determined by a pH meter (Metrohm, Herisau, Switzerland).

Concentrations of polyethylene glycol and PSP were measured and, after correction for the amounts removed proximally, were used to calculate intraluminal volume flow rates and delivery rates of nutrients and PSP to intestinal sites as described previously.¹⁹⁻²² Cumulative duodenal delivery of PSP was used to assess gastric liquid meal emptying. The intervals from meal intake to cumulative duodenal delivery of 20%, 50%, and 90% of cumulative PSP delivery to the duodenal site were used as a measure of early, middle, and late gastric liquid meal emptying times, respectively. The latency between duodenal and ileal PSP deliveries (50% of cumulative quantity recovered) was used to calculate small intestinal transit time.

Plasma cholecystokinin (CCK) was determined by radioimmunoassay using antibody T204, which is directed to the sulfated tyrosyl region. Its cross-reactivity with sulfated forms of gastrin is negligible (<2%), and it does not bind to unsulfated gastrins or structurally unrelated peptides. The detection limit of the assay is 0.5 pmol/L, and intra-assay and interassay precisions are <8% and <15%, respectively.^{23,24}

Radioimmunoassay of peptide YY in plasma was performed using antiserum code no. 8412-2 (a gift from R. Ekman, Department of Neurochemistry, University of Lund, Lund, Sweden) raised in rabbits against the N terminus of peptide YY as described previously²⁵ but without conjugation to the carrier protein.²⁶ The antibody cross-reacts 100% with human peptide YY. Synthetic human peptide YY (Peninsula Laboratories Europe Ltd., Merseyside, St. Helen's, England) was used for standards and for preparation of ¹²⁵I-peptide YY, which was labeled according to the stoichiometric chloramine T method and purified using high-pressure liquid chromatography.²⁵ Detection limit of the assay was <1 pmol/L, and 50% inhibition was obtained with 23 pmol/L peptide YY. Recovery of peptide YY added to plasma in concentrations between 5 and 50 pmol/L deviated <15% from expected values. Intra-assay coefficient of variation was <5%. The antibody showed no cross-reaction with human neuropeptide Y or human pancreatic polypeptide at concentrations of up to 500 pmol/L.

Glucagon-like peptide 1 (GLP-1) immunoreactivity was measured as described previously.²⁷ Antiserum 390 was raised against a synthetic C-terminal decapeptide of amidated GLP-1 (proglucagon 98-107) amide coupled to bovine serum albumin with carbodiimide.²⁵ The antiserum requires carboxy-terminal amidation for binding and cross-reacts fully with GLP-1 (72-107) amide but not with C-terminally extended or deleted forms of GLP-1; it does not cross-react with any other members of the glucagon/secretin family of peptides. The experimental detection limit in plasma is approximately 1 pmol/L, and the intra-assay coefficient of variation is <6%. Before radioimmunoassay, plasma samples were extracted with

Table 2. Cumulative Postprandial Delivery of Nutrient to Small Intestinal Sites and Gastric Emptying Times (20%, 50%, and 90% of the meal marker PSP, respectively) and Small Intestinal Transit Time

	Normal subjects		Pancreatic insufficiency	
	Placebo	Enzymes	Placebo	Enzymes
Nutrient delivery				
Duodenum (kJ)	318 ± 67	328 ± 48	639 ± 222 ^a	381 ± 149 ^b
Jejunum (kJ)	113 ± 38	126 ± 42	557 ± 198 ^a	308 ± 131 ^b
Ileum (kJ)	69 ± 21	72 ± 29	487 ± 212 ^a	227 ± 105 ^b
Motor responses				
Duration of fed pattern (min)	196 ± 22	207 ± 34	131 ± 14 ^a	170 ± 17 ^b
Gastric emptying (20%) (min)	24.7 ± 3.3	25.2 ± 2.8	36.5 ± 4.1	29.5 ± 3.6
Gastric emptying (50%) (min)	59 ± 6	60 ± 7	66 ± 8	63 ± 8
Gastric emptying (90%) (min)	163 ± 12	159 ± 14	128 ± 10 ^a	148 ± 14 ^b
Small intestinal transit (min)	86 ± 9	85 ± 10	44 ± 6 ^a	62 ± 6 ^b

NOTE. Values are expressed as \pm SE from normal subjects ($n = 14$) and patients with pancreatic insufficiency ($n = 12$) with placebo vs. pancreatic enzyme supplementation.

^a $P < 0.001$ vs. normal subjects.

^b $P < 0.01$ vs. placebo.

ethanol (final concentration, 70%, vol/vol). The recovery of GLP-1 added to plasma before extraction was $78\% \pm 8\%$ (mean \pm SD).

Digestive and interdigestive motility patterns were identified and analyzed by visual inspection as described previously. Specifically, phase III motility was defined as uninterrupted periods of regular contractions (10–12 per minute) for at least 2 minutes, with distal propagation to at least one further recording site.¹⁰ In addition, antral and duodenal motor activities were quantified by computer assistance and expressed in a motility index defined as $\ln[\text{AUC} + 0.5]$. The duration of the digestive period was defined as the interval between ingestion of the test meal and the termination of the fed motor pattern, i.e., occurrence of the next proximal interdigestive phase III, at the duodenal recording site.^{28,29}

Statistical analyses were performed by using t tests for paired (comparisons within subjects: preprandial vs. postprandial, enzyme vs. placebo supplementation, and ileal nutrient vs. saline perfusion) or unpaired (comparisons between normal subjects and patients) data, respectively. Responses to ileal nutrient vs. saline perfusions were compared by using the nonparametric Wilcoxon signed-rank test for paired data.³⁰ Data are expressed as means \pm SE, unless indicated otherwise.

Results

Protocol 1: Postprandial Motility and Luminal Nutrient Delivery

Motility patterns. In normal subjects, the fed motor pattern persisted for 196 ± 22 minutes after the start of the meal with placebo (Table 2 and Figure 1) and was then followed by a phase III of the interdigestive motor complex originating in the duodenum or proximal jejunum; in no case did it originate in the antrum. A similar duration of fed motility was observed with pancreatin supplementation (Table 2).

Patients with pancreatic insufficiency maintained a fed motility pattern for 131 ± 14 minutes after the placebo meal, which was significantly shorter compared with normal subjects ($P < 0.001$; Table 2 and Figure 2). In the same patients, pancreatin supplementation with the meal was associated with a longer duration of fed pattern compared with placebo (170 ± 17 minutes; $P = 0.016$; Table 2 and Figure 3). At the termination of the fed period, mean nutrient flow rate was 984 ± 518 J/min in the duodenum and 1062 ± 498 J/min in the ileum (Figure 3).

In contrast to the duration of fed pattern, motility indices within the postprandial period were similar in normal subjects and patients (6.23 ± 0.13 and 6.10 ± 0.37 , respectively) and were not influenced by addition of enzymes to the meal (6.30 ± 0.14 and 6.21 ± 0.11 , respectively). Similarly, characteristics of the first interdi-

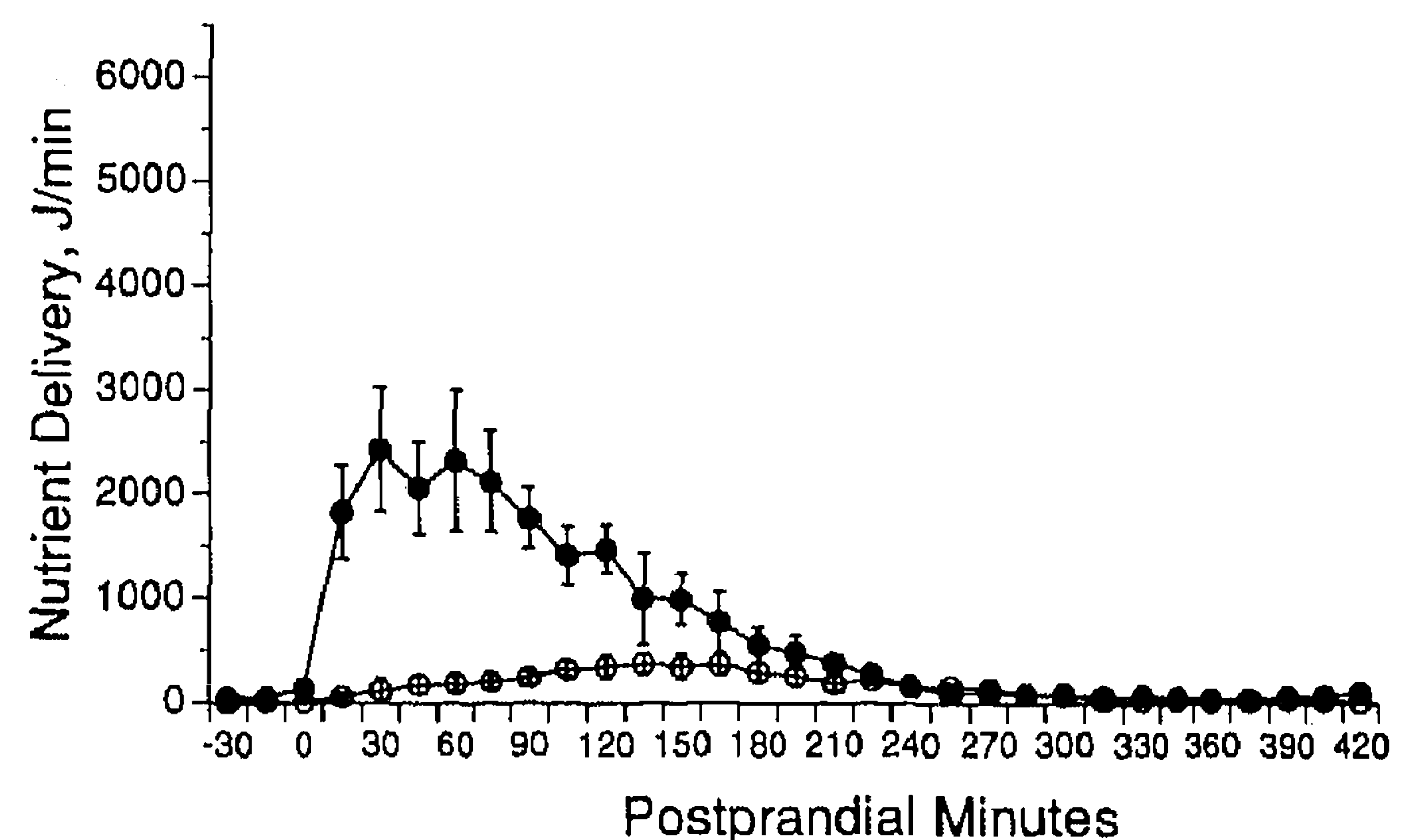


Figure 1. Duration of fed motor pattern and delivery of nutrient to duodenum (●) and ileum (○) in 14 normal subjects after ingestion of a test meal (1257 kJ) at 0 hours.

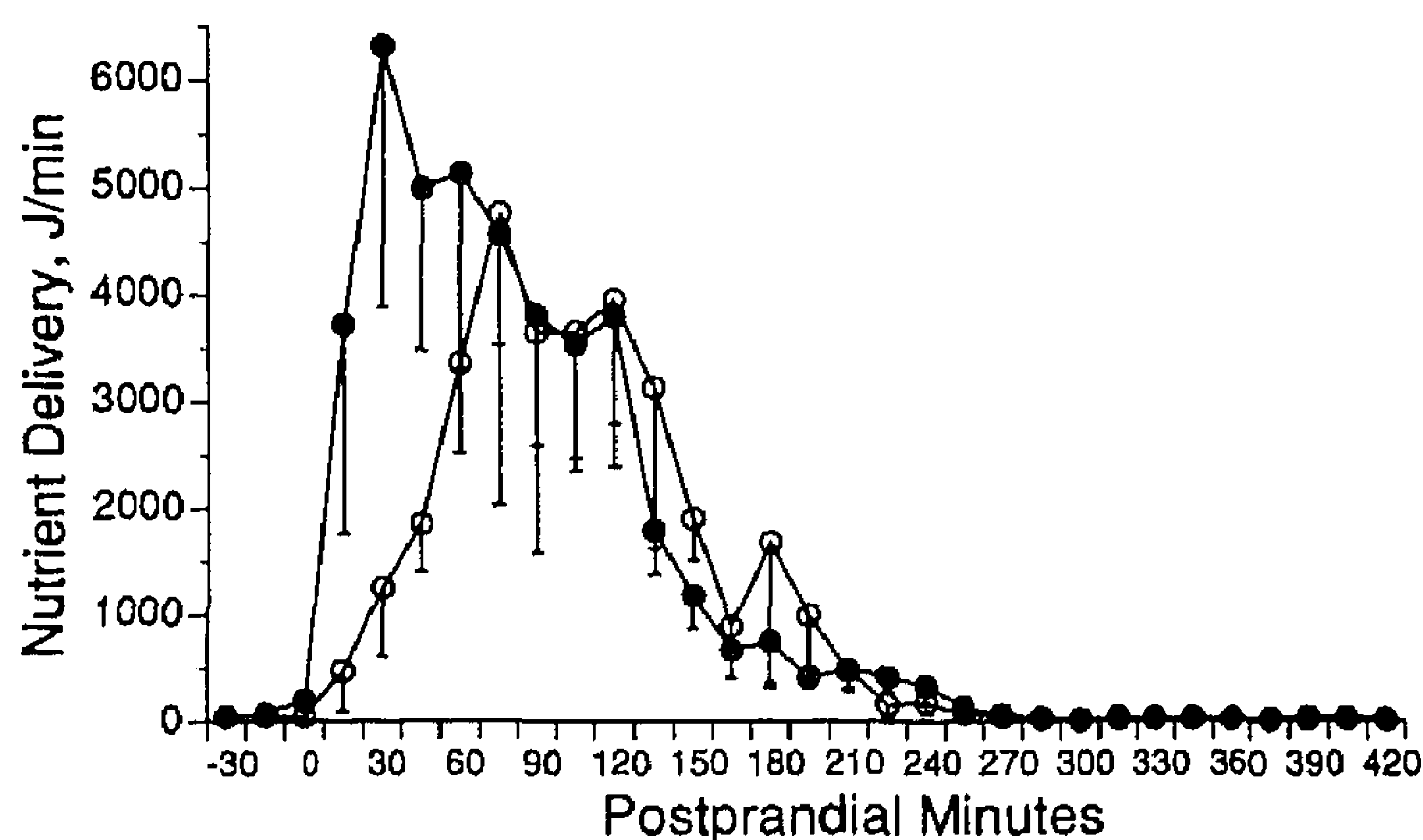


Figure 2. Duration of fed motor pattern and delivery of nutrient to duodenum (●) and ileum (○) in 12 patients with untreated pancreatic insufficiency after ingestion of a test meal (1257 kJ) at 0 hours.

gestive phase III did not differ between normal subjects and patients (duration, 6.9 ± 1.2 vs. 7.5 ± 2.1 minutes; propagation velocity, 4.5 ± 0.6 vs. 4.1 ± 0.7 cm/min, respectively). Again, there was no effect of pancreatin supplementation.

Cumulative luminal nutrient and marker delivery. In normal subjects, nutrient delivery to intestinal sites was not affected by addition of pancreatic enzymes to the test meal; under both conditions, cumulative energy loads to the duodenum, jejunum, and terminal ileum were about 25%, 10%, and 6% of the energy content of the meal ingested, respectively (Table 2 and Figure 1).

In patients with pancreatic insufficiency without enzyme supplementation (i.e., placebo), nutrient delivery to all intestinal sites was significantly increased compared with healthy subjects ($P < 0.001$; Table 2 and Figure 2); cumulative duodenal, jejunal and ileal energy loads were about 51%, 44%, and 39% of total, respectively.

When pancreatic enzymes were administered together with the meal, duodenal, jejunal, and ileal nutrient deliveries in patients were decreased to 30%, 27%, and 18% of total, respectively ($P < 0.001$ vs. placebo; Table 2 and Figure 3).

Cumulative gastric emptying of 20% of the marker tended to occur later in untreated patients compared with healthy subjects ($P = 0.06$), but emptying of 50% occurred at similar rates in both normal subjects and patients (Table 2). By contrast, late (90%) gastric emptying rates were consistently and markedly increased in patients compared with controls ($P < 0.001$). Thus, the interval between meal ingestion and emptying of 90% of the meal was shortened by nearly 30% compared with normals (Table 2). Similarly, small intestinal transit occurred faster in pancreatic insufficiency without enzyme

supplementation; transit velocity was nearly doubled compared with healthy controls ($P < 0.001$; Table 2).

Enzyme supplementation had no effect in normal subjects. By contrast, in pancreatic insufficiency, enzyme supplementation decelerated both late gastric emptying and small intestinal transit (both $P < 0.01$ vs. placebo), although rates did not reach values observed in normal subjects (Table 2).

In both normal subjects and patients, cumulative recoveries of the meal marker PSP were similar under all experimental conditions and were between 78% and 97% of the amount administered. There was a consistent tight correlation between duodenal deliveries of PSP and energy (in each experiment, $r > 0.9$ and $P < 0.001$).

Luminal nutrient flow at end of digestive period.

At the time of the termination of the fed period, i.e., at the occurrence of the first interdigestive motor pattern, normal subjects had mean luminal nutrient flow rates of 486 ± 62 J/min in the duodenum and 265 ± 72 J/min in the ileum (Figure 1). Ileal energy was composed of 39% carbohydrate, 46% protein, and 15% lipids.

By contrast, in patients with placebo-treated pancreatic insufficiency, mean nutrient flow rates at the end of the fed period were nearly four times greater in the duodenum (1796 ± 417 J/min) compared with normal subjects ($P < 0.001$), and ileal nutrient exposure was increased 10-fold (2575 ± 1014 J/min; $P < 0.001$ vs. normals; Figure 2). In untreated patients, ileal energy was composed of 52% carbohydrate, 14% protein, and 34% lipids.

Plasma glucose and hormone responses. Plasma glucose increased from preprandial values of 93 ± 3 to 126 ± 4 mg/dL at 60 minutes after the meal in normal subjects; there was no effect of enzyme supplementation (not shown). In patients with chronic pancreatitis, plasma glucose increased after the placebo meal from 99 ± 6 to 132 ± 8

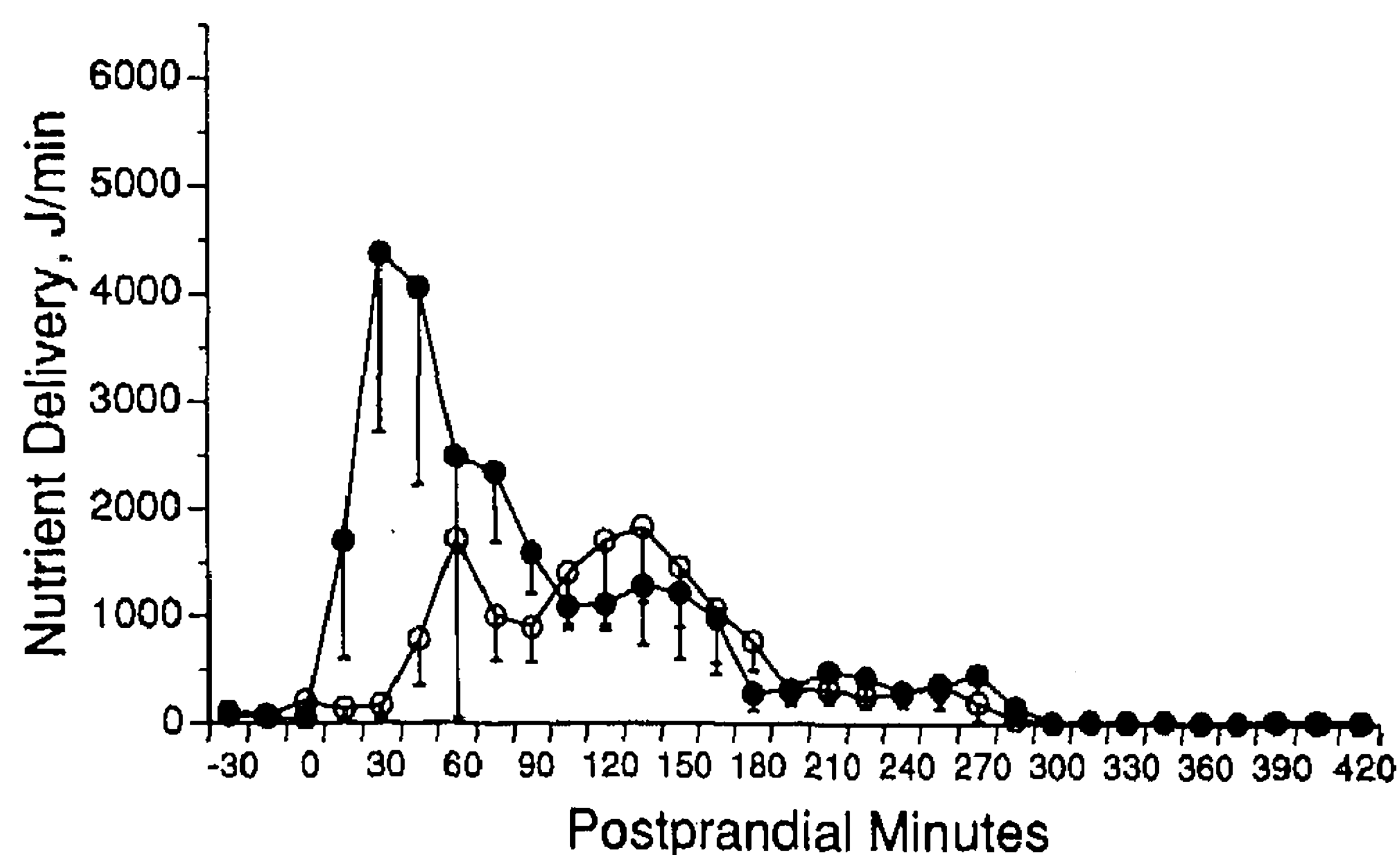


Figure 3. Duration of fed motor pattern and delivery of nutrient to duodenum (●) and ileum (○) in 12 patients with pancreatic insufficiency after ingestion of a test meal (1257 kJ) together with pancreatic enzyme supplementation at 0 hours.

Table 3. Plasma CCK, Peptide YY, and GLP-1: Preprandial and Postprandial Peak Concentrations and Integrated Incremental Responses in Healthy Subjects and Patients With Pancreatic Insufficiency Without and With Pancreatic Enzyme Supplementation

	Normal subjects (n = 14)		Pancreatic insufficiency (n = 12)	
	Placebo	Enzymes	Placebo	Enzymes
CCK				
Preprandial	2.0 ± 0.4	1.9 ± 0.4	2.3 ± 0.5	2.2 ± 0.5
Postprandial peak (pmol/L)	5.7 ± 0.8	6.1 ± 1.1	4.3 ± 0.8	5.3 ± 1.1
Integrated incremental response over preprandial (ΔEpmol/L · 180 min)	453 ± 67	471 ± 75	249 ± 36 ^a	420 ± 58 ^b
Peptide YY				
Preprandial	1.5 ± 0.3	2.1 ± 0.4	3.6 ± 0.5	3.1 ± 0.5
Postprandial peak (pmol/L)	4.6 ± 1.5	5.9 ± 2.7	8.5 ± 1.7	6.8 ± 1.4
Integrated incremental response over preprandial (ΔEpmol/L · 180 min)	351 ± 87	447 ± 135	1048 ± 184 ^a	665 ± 252
GLP-1				
Preprandial	8.5 ± 1.1	9.6 ± 1.2	10.4 ± 2.2	12.0 ± 1.9
Postprandial peak (pmol/L)	25.0 ± 4.3	21.5 ± 4.1	52.0 ± 11.3 ^a	32.0 ± 5.5 ^b
Integrated incremental response over preprandial (ΔEpmol/L · 180 min)	1545 ± 501	1424 ± 489	4584 ± 1050 ^a	2970 ± 546 ^b

NOTE. For each peptide there was a significant ($P < 0.01$) increase over baseline in response to the meal with both placebo and enzymes in normals and patients. Values are expressed as means ± SE.

^a $P < 0.01$ vs. normal subjects.

^b $P < 0.01$ vs. placebo.

mg/dL and after the meal with pancreatin from 97 ± 7 to 136 ± 9 mg/dL.

Preprandial CCK plasma concentrations were similar before both meals in all participants and did not differ between normal subjects and patients (Table 3). Postprandially, plasma CCK increased about threefold in healthy individuals after both placebo and pancreatin meals ($P < 0.01$). In patients, the prandial peak increase in plasma CCK was about twofold after the placebo meal, and the integrated CCK response was significantly smaller than in healthy subjects ($P < 0.002$). By contrast, pancreatin supplementation was associated with a significantly greater prandial CCK response compared with placebo ($P < 0.01$; Table 3).

In all subjects plasma peptide YY increased postprandially ($P < 0.01$). There was an insignificant trend towards greater plasma peptide YY concentrations in patients compared with healthy subjects both before the meal and for postprandial peak values (Table 3); on the other hand, the integrated incremental response to the placebo meal was significantly greater in untreated patients ($P < 0.001$) but not in treated patients compared with healthy subjects (Table 3).

Before the meals, GLP-1 plasma levels were similar in normal subjects and patients (Table 3). GLP-1 concentrations increased in response to the meal in all subjects ($P < 0.01$). There was no difference between responses between placebo and enzyme meals in normals. In patients, postprandial peak values and integrated incremen-

tal responses to the placebo meal were significantly greater than in healthy subjects ($P < 0.001$); this excessive increase was partially reverted by enzyme supplementation (Table 3).

Protocol 2: Effect of Ileal Nutrient Perfusion on Fed Motility

Duodenal perfusion with essential amino acids induced a persistent fed motility pattern at all small intestinal sites in each subject. Intestinal motor activities were similar before either ileal perfusion both in healthy individuals and in patients with pancreatic insufficiency.

Pattern and activity index of digestive motility were not altered by ileal saline perfusion in either normals or patients (Figures 4A and 5A). By contrast, ileal nutrient perfusion induced marked intestinal motility changes in both groups. In the presence of continuing endogenous stimulation, seven of eight ileal nutrient perfusions (in contrast to zero of eight ileal saline perfusions; $P < 0.01$) in normal subjects and four of five nutrient perfusions (vs. zero of five saline perfusions; $P < 0.05$) in patients were followed by a phase III-like motor activity front originating in the duodenum or proximal jejunum after a mean of 17.8 ± 6.7 minutes in normals and 21.6 ± 7.2 minutes in patients (Figures 4B and 5B); there was no antral involvement. These activity fronts were propagated distally with a mean migration velocity of 3.9 ± 0.6 or 4.2 ± 0.8 cm/min, respectively, and were always followed by a period of motor quiescence (phase I-like

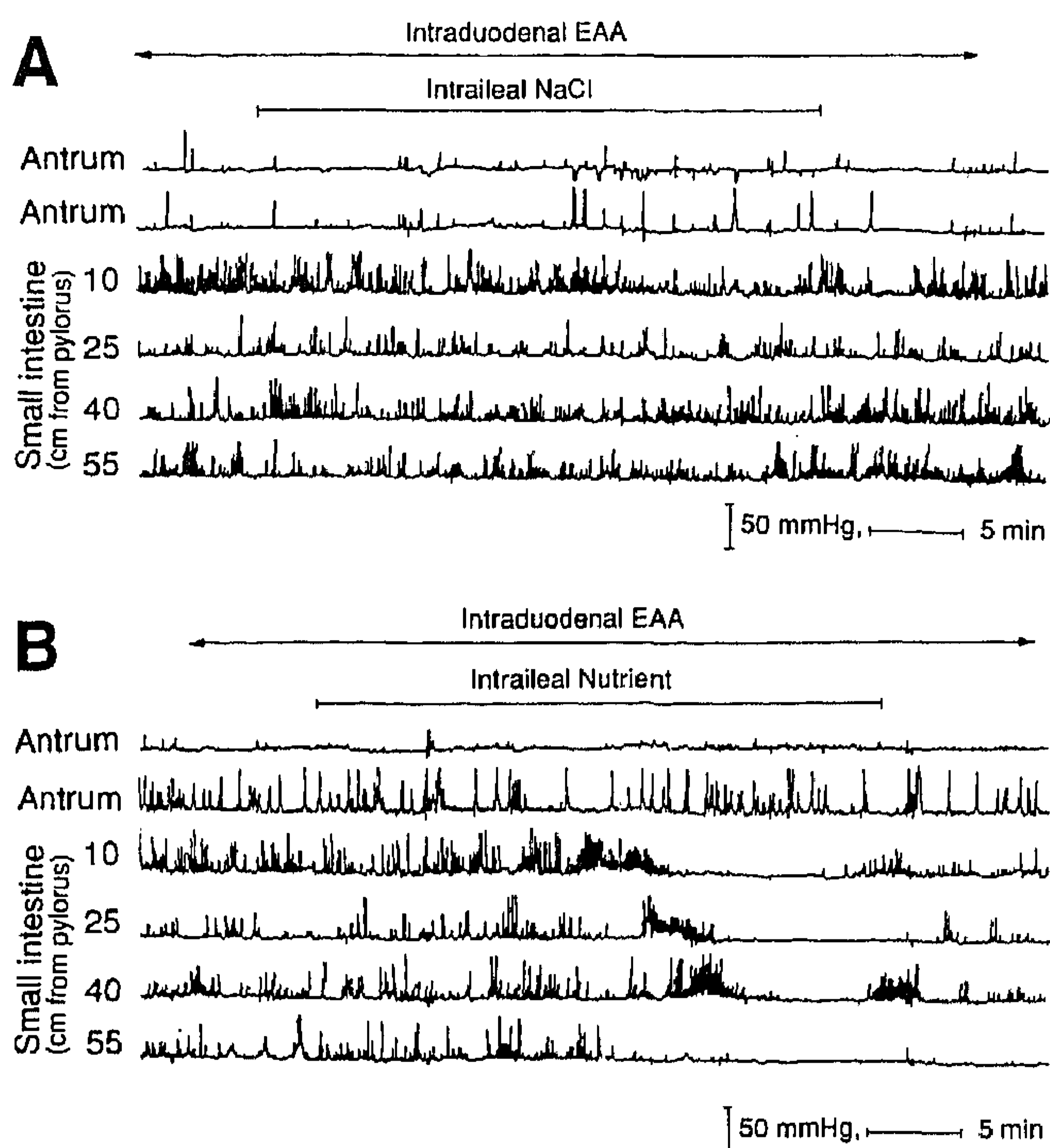


Figure 4. Effects of ileal perfusion with (A) NaCl and (B) nutrient on intestinal motility in a single healthy subject. A fed motor pattern induced by continuous duodenal perfusion with essential amino acids (EAA) was maintained in response to ileal NaCl but was disrupted by ileal nutrient. The fed pattern was replaced by a migrating motor activity front followed by motor quiescence.

activity) for another 13.1 ± 2.1 minutes or 10.6 ± 3.2 minutes, respectively. Decreased motor activity was always observed in response to ileal nutrient, including in the two individuals in whom no phase III-like activity occurred.

Discussion

The major findings of this study can be summarized as follows. First, the gastrointestinal motor response to a liquid low-energy meal differed in patients with severe pancreatic exocrine insufficiency compared with normal subjects. Transit of chyme (gastric emptying and small intestinal transit) was accelerated, and the duration of fed pattern was shortened, resulting in earlier transition to the subsequent interdigestive pattern. Second, these motor changes were reversed by enzyme supplementation with the test meal, i.e., decreased malabsorption, suggesting that the altered motor response was associated with or caused by increased nutrient delivery to the distal intestine. Third, analogous motility changes were reproduced by perfusing nutrients into the ileal lumen; despite continuous endogenous stimulation, fed motor activity responded by conversion into an interdigestive-like pattern both in healthy subjects and in patients with pancreatic exocrine insufficiency.

Duodenal exposure to nutrients is a major mechanism inducing the digestive motility response. By contrast, mechanisms regulating the end of the digestive period and the transition to the subsequent interdigestive period are unknown (besides late-postprandial disappearance of stimulatory nutrients from the proximal intestinal lumen). However, there is evidence that regulatory mechanisms may be recruited late postprandially by the distal intestine that may facilitate or induce the conversion from the digestive to the interdigestive state. In several species including humans, increased ileal nutrient exposure decreases stimulated motor and secretory functions into the basal range.^{9-12,20,31-38}

As an implication, clinical malabsorption syndromes, such as end-stage chronic pancreatitis, may be associated with abnormal motility responses. However, only a few studies have investigated gastrointestinal motility in chronic pancreatitis, with equivocal observations. Inter-

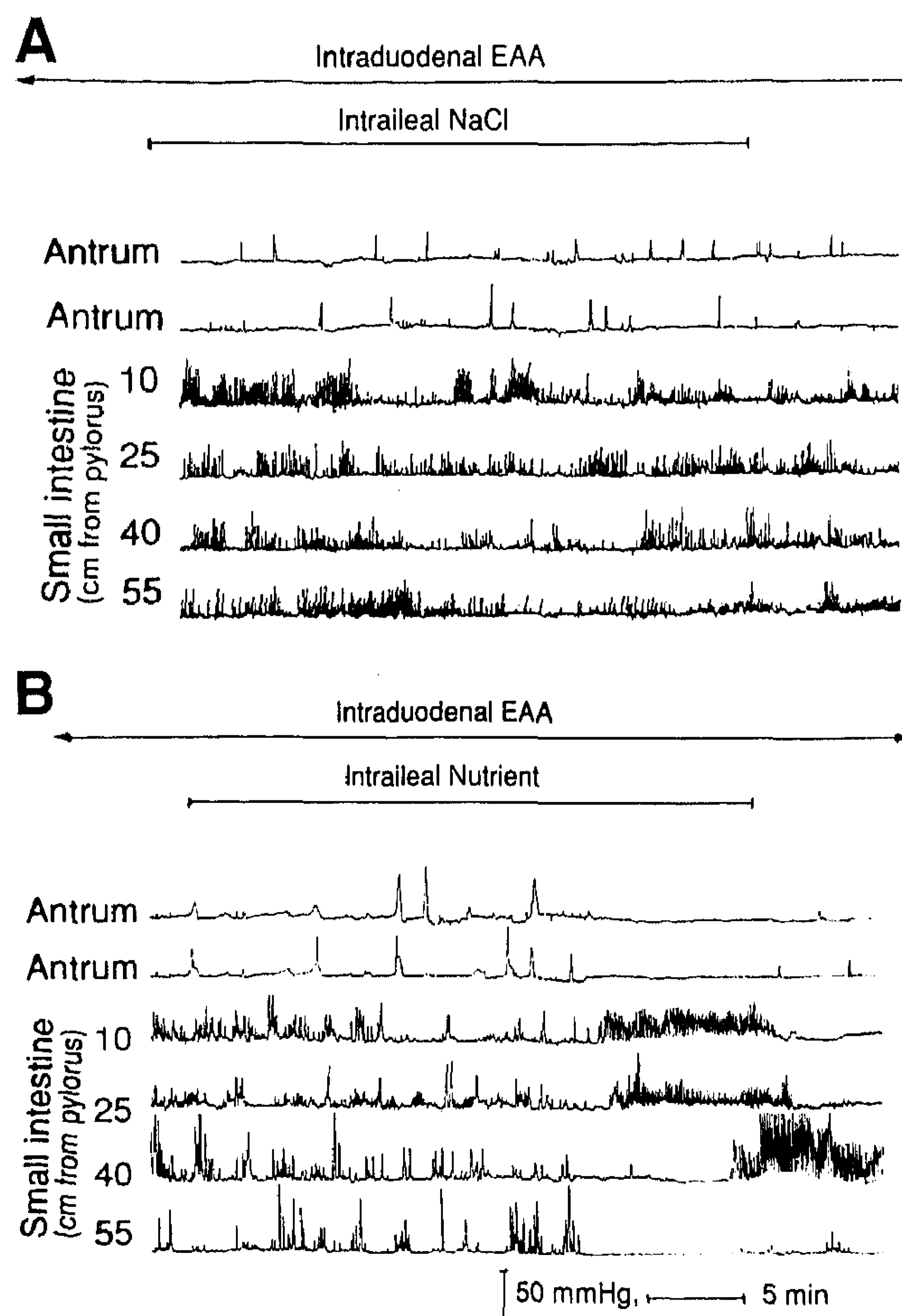


Figure 5. Effects of ileal perfusion with (A) NaCl and (B) nutrient on intestinal motility in a patient with pancreatic insufficiency. The fed pattern induced by intraduodenal amino acid (EAA) perfusion remained unchanged during ileal NaCl perfusion; by contrast, ileal nutrients induced phase III-like motor activity and subsequent motor quiescence.

digestive antral motility was reported to be enhanced in patients with chronic pancreatitis,⁶ but normal duodenal activity was observed in another study.³⁹ In pancreatectomized dogs, interdigestive antral but not duodenal motor activity was increased compared with normal controls.⁴⁰

Similarly, it is unclear if postprandial motility is altered. Gastric emptying has been reported to be accelerated in patients with pancreatic insufficiency,⁵ but this was not confirmed in a subsequent investigation when emptying rates were corrected for gastric volume output.⁷ In a less homogenous patient population with varying degrees of insufficiency, increased gastric emptying rates late postprandially and decreased proximal intestinal transit rates were reported; however, distal intestinal nutrient deliveries, manometric responses, and effects of enzyme supplementation were not studied.⁴ In another study, postprandial antral motility was unchanged, but gastric emptying and intestinal nutrient deliveries were not determined.⁶ The original notion of accelerated gastric emptying in pancreatic insufficiency in the absence of active inflammation was strengthened recently by findings in an experimental dog model.⁴¹

We now report markedly altered gastrointestinal motility responses to a liquid low-energy meal in patients with severe pancreatic insufficiency. Gastric emptying and small intestinal transit were more rapid, and the duration of the fed motor pattern was significantly shortened compared with healthy subjects. Decreased transit time through the proximal gastrointestinal tract, i.e., shorter nutrient exposure of the stimulatory segments of the gut, contributed to the shorter length of the digestive period.

On the other hand, at the time of (premature) termination of the fed pattern in untreated patients, gastric emptying was incomplete and duodenal nutrient exposure was fourfold greater than required to maintain fed motility in normal subjects. These observations suggest either that the overall generation of or responsiveness to luminal stimuli may be decreased in these patients and/or that additional inhibitory mechanisms were activated by increased nutrient delivery into the distal small bowel, which counterbalanced the stimulatory effects of duodenal nutrient exposure and induced premature conversion from the fed to the interdigestive motility state. The latter explanation was supported by the observation that enzyme supplementation that decreased malabsorption also reverted motility changes.

To test the hypothesis that ileal nutrient exposure participates in the regulation of the fed-interdigestive transition, we perfused nutrient intraileally in normal subjects and patients with pancreatic insufficiency and determined effects on endogenously stimulated motility.

As stimulus, we used continuous intraduodenal essential amino acid perfusion at an established rate that was known to induce fed motor and secretory responses¹⁰ and with an energy load similar to that present in the duodenal lumen in the third postprandial hour. Although theoretically it might have been preferable to use mixed nutrients as the stimulus, such a perfusate may be partly delivered to the distal lumen, thus confounding experimental conditions.

Because under the specific experimental conditions of this study ileal nutrients disrupted the fed pattern and induced an interdigestive-like motor pattern in the majority of both normals and patients, we conclude that, in the presence of weak endogenous duodenal stimulation, increased ileal nutrient exposure may induce or facilitate conversion from the digestive into the interdigestive state. This suggests that in pancreatic insufficiency, increased delivery of malabsorbed nutrient to the distal intestine contributed to the earlier transition from the digestive into the subsequent interdigestive period.

On the other hand, in normal subjects, luminal, especially intraileal, nutrients delay (rather than accelerate) gastric emptying^{20,33,42} and small intestinal transit ("ileal brake"^{11,12}). Therefore, the observation of accelerated gastric emptying and small intestinal transit in untreated pancreatic insufficiency and increased postprandial nutrient concentrations throughout the small intestinal lumen suggests that additional regulatory mechanisms may be altered.

It might be argued that disturbed motor regulation in patients may have been caused by alcoholic or diabetic autonomic neural alterations. However, there was no evidence for autonomic dysfunction in any of the patients, and motor responses did not differ among diabetic and nondiabetic patients, or among alcoholic and idiopathic chronic pancreatitis. Prandial blood glucose levels may also have influenced gastric emptying⁴³⁻⁴⁵ but were similar in normal subjects and patients throughout the study. An underlying motor disturbance is unlikely because manometric motility patterns were normal in both the digestive and interdigestive periods, which is similar to what has been reported by others.^{6,46} Finally, because enzyme supplementation partially reverted motility changes in patients, it is likely that the responsible mechanism involves malabsorbed nutrients rather than a pre-existing motor disturbance.

Whether motor changes in response to decreased digestion and/or increased distal intestinal nutrient delivery are mediated by diminished release of regulatory peptides remains uncertain. Lack of endogenous pancreatic polypeptide release caused by pancreatic insufficiency^{6,46} may contribute to motility changes. Indeed, in dogs,

exogenous pancreatic polypeptide prolonged the fed-motor pattern.⁴⁷ However, this hypothesis would not explain why enzyme treatment reverted motor changes in our study.

Another candidate mechanism is decreased postprandial release of CCK, which is believed to participate in inducing and maintaining the fed state and to be a physiological inhibitor of gastric emptying.⁴⁸ We observed that, in our patients with severe untreated pancreatic insufficiency, CCK release in response to the liquid test meal was decreased but was restored by enzyme supplementation. These findings are explained by slower luminal generation of stimulatory digestion products and confirm earlier studies using different test meals.⁴⁹⁻⁵¹ Thus, a diminished postprandial CCK response in pancreatic insufficiency accelerates gastric emptying. However, an exclusive role of decreased CCK release is unlikely for the following two reasons. First, even complete CCK-receptor blockade by a selective CCK-receptor antagonist causes only moderate (about 40%) acceleration of human gastric emptying of a liquid mixed meal very similar to the one used by us.⁴⁸ It is unlikely that the comparatively small difference in CCK release observed in our study could have been the sole mechanism responsible for the pronounced motor effects. Second, differences in CCK responses occurred within the first 2 postprandial hours when gastric emptying rates did not differ. Therefore, although decreased CCK release may contribute to the observed differences, it is unlikely that it is the only mechanism.

Late-postprandial motor events may also be regulated by hormones released from the distal gut, such as peptide YY or GLP-1,⁵² in response to increased nutrient delivery. We found both peptide YY and GLP-1 to be increased in pancreatic insufficiency after the placebo meal compared with controls, which is similar to previous reports.^{53,54} Excessive release of both peptides was partially reversed by enzyme supplementation, suggesting that increased delivery of nutrients to the distal intestine was responsible. However, whether peptide YY or GLP-1 participate as regulators is uncertain because both retard rather than accelerate gastrointestinal transit.^{55,56}

For methodological reasons, a liquid meal was used instead of a (more physiological) solid-liquid meal, and our conclusions need to be limited to these experimental conditions. In particular, we did not address the issue whether the transition from postprandial to interdigestive motility may also be regulated by ileal nutrients under normal conditions. In our healthy individuals, the meal was absorbed rapidly and nearly completely, and the resulting physiological malabsorption was far lower compared with what is known from more regular

meals.⁵⁷⁻⁵⁹ Furthermore, it remains speculative if in patients with pancreatic insufficiency motility changes occur after meals of different composition and if they have additional pathophysiological implications: nutrient absorption may be further compromised because of accelerated transit and decreased mucosal chyme exposure. Moreover, such motor disturbances may explain why in some patients postprandial abdominal symptoms respond to enzyme therapy.

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