Resection and palliation of pancreatic and periampullary carcinoma
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CHAPTER 6

Intragastric and intestinal pH profiles
after pylorus preserving pancreaticoduodenectomy

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Submitted
Abstract

Background: Pylorus preserving pancreaticoduodenectomy (PPPD) is a major surgical procedure that affects gastrointestinal function. The long-term effect of PPPD on gastrointestinal pH profiles is unknown. Therefore we have analysed gastrointestinal pH in patients after PPPD in comparison to healthy controls.

Methods: In the period between October 1999 and May 2000, 16 patients (m/f: 9/7; age 46-78 yr) and 9 healthy control subjects (m/f: 5/4; age 20-54 yr) were studied. The median period between PPPD and measurement was 3.1 years (range 1.7-6.5 years). Patients and volunteers underwent 24 hour ambulatory continuous intragastric and intestinal pH measurements under standardised conditions.

Results: Median 24h intragastric pH of patients and healthy controls was 1.7 (IQR 1.6-2.1) and 1.7 (IQR 1.5-2.0), respectively (NS). Median 24h intestinal pH in patients was significantly (p<0.04) higher in patients compared to healthy control subjects, 6.3 (IQR 6.0-6.5) versus 6.0 (IQR 5.9-6.1), respectively, resulting mainly from differences in the nocturnal period. There were no differences between patients and healthy controls in postprandial intragastric pH, postprandial intestinal pH, or median daytime pH.

Conclusion: Median 24h intragastric pH in patients after PPPD is not different from healthy controls. Median intestinal pH in patients after PPPD was not lower, but instead, significantly higher compared to healthy controls resulting mainly from differences in the nocturnal period.
**Introduction**

The pylorus preserving pancreaticoduodenectomy (PPPD) is a major surgical procedure performed for pancreatic and periampullary malignancies or chronic pancreatitis. This resection may interfere with the complex mechanisms that regulate nutrient digestion such as gastrointestinal motility and secretion. Gastrointestinal pH has a major influence on nutrient digestion since solubilisation of fat and pancreatic enzyme activity are both pH dependent. Previous studies have shown that patients with chronic pancreatitis have a lower postprandial intragastric and intraduodenal pH because of alterations in feedback on acid secretion. After PPPD, patients are deprived of the larger part of their duodenum. Only a small proximal rim of 2 cm remains in situ. The resection of the larger part of the duodenum may reduce or even eliminate its inhibitory effect on intragastric acidity which is supposed to be mediated by CCK as enterogastrone.

After PPPD some patients without tumour recurrence lose weight while they are treated with enzyme supplementation. We hypothesise that patients after PPPD have an increased gastric acid production and thus a lower intragastric and intestinal pH. This may negatively affect nutrient digestion and absorption even during enzyme supplementation. Data on the actual intragastric and intestinal pH after PPPD are not available but are needed for clinical reasons. Better knowledge and insight may contribute to further improvements of the pharmacological treatment of maldigestion after PPPD. Aim of the study was to evaluate the intragastric and intestinal pH profiles in patients who underwent PPPD and to compare results with those obtained in healthy volunteers.

**Patients and Methods**

**Patients**

In the period between October 1999 and May 2000, 16 patients (9 male, 7 female; age 46-78 years) and 9 healthy control subjects (5 male, 4 female; age 20-54 years) were studied. PPPD was performed for ampullary carcinoma in 10 patients, and for chronic pancreatitis in 6 patients. At the time of the study, none of the patients had any sign of tumour recurrence. The median period between PPPD and pH-metry was 3.1 years (range 1.7-6.5 years).

**Protocol**

Patients and volunteers underwent twenty-four hour ambulatory continuous intragastric and intestinal pH measurements. Medication affecting gastrointestinal motility and secretion was stopped three days prior to the measurements. After an overnight fast, patients and control subjects came to the hospital in the morning. In the patients a single lumen catheter was passed transnasally into the stomach and from there it was positioned in the jejunum, 10-15 centimetres past the pylorus, under fluoroscopic control with the help of a guide wire. In healthy control subjects the catheter was placed in the horizontal part of the duodenum near the Treitz ligament 10-15 cm distal of the pylorus. A glass membrane pH electrode was passed through the catheter until the tip of the electrode was at least two centimetres outside of the catheter. A second glass
membrane pH electrode was passed transnasally through the same nostril and positioned in the gastric corpus 10 cm below the esophagogastric junction (figure 1).

During the twenty-four hour recording period, time of meal ingestion (lunch at 14.00 hours, dinner at 18.00 hours, breakfast at 8.00 hours) and supine period (23.00 hours to 7.00 hours) were fixed. All subjects received a standardised hospital lunch (32 g protein, 24 g fat, 65 g carbohydrates, 600 kcal) and evening meal (29 g protein, 32 g fat, and 75 g carbohydrates, 700 kcal). All subjects stayed in hospital during the day until 19.00 hours and were allowed to return home until 11.30 hours the next morning. In the morning patients ate a standard hospital prepared breakfast (identical to the lunch). After the twenty-four hour period the position of the electrodes was checked again by fluoroscopy before removing them.

Figure 1. Position of the intragastric and intrajejunal pH catheters in a patient after pylorus preserving pancreaticoduodenectomy.

Intraluminal pH monitoring

Intragastric and intestinal pH were simultaneously measured by miniature glass electrodes. Intragastric pH was measured by a 3 mm glass probe with an internal reference electrode (model 440M3, W. Ingold AG, Urdorf, Switzerland). Intestinal or intraduodenal pH was measured by a 1.5 mm glass probe (W. Ingold AG, Urdorf, Switzerland) with the internal reference electrode of the 3 mm probe as a reference. The pH electrodes were connected to two portable dataloggers, each with an exchangeable 96 kByte memory (Gastrograph Mark II, Medical Instruments Corporation AG, Solothurn, Switzerland). The sampling rate was 4 per second. Every 2 seconds the median of 8 voltage measurements was calculated and stored in the memory (43200 readings in 24 hours for each pH probe). Response time, sensitivity and drift of the pH electrodes were
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tested before each measurement. The electrodes and dataloggers were calibrated before and after the measurement period at 37°C using buffer solutions of pH 7 and pH 1.67; check of the slope was performed with buffer solution of pH 4.01. An electrode drift of less than 0.15 pH units was considered acceptable. After completion of the post-measurement calibration the data were transferred to an IBM compatible personal computer using a software program provided by the manufacturer (MIC AG). Evaluation of the raw data was performed by a software program developed and validated by our team.

Pancreatic function analysis
Patients underwent an exocrine pancreatic function test during the 24 hour period of the pH measurements. During lunch patients consumed 1 gram of N-benzoyl-L-tyrosyl-P-amino benzoic acid (NBT-PABA). The urine was collected for a period of 6 hours following consumption of NBT-PABA and the 6 hour urinary PABA recovery was determined. A PABA recovery of more than 50% was considered normal. In addition stool was collected for 24 hours following lunch and the 24-hour faecal fat excretion was assessed. A fat excretion of less than 7 gram per 24 hours was considered normal.

Data analysis
Data analysis and statistics were based on median pH values of 6 seconds. Median pH values, interquartile ranges (IQR, i.e. values between the 25th and 75th percentile) and percentages of time that pH values were below pH thresholds 3 and 5 were calculated for individuals and groups over the twenty-four hour period and two postprandial periods (lunch, dinner) of 60 and 120 minutes. Differences in intraluminal pH between the groups were analysed by a Mann-Whitney U analysis. The Pearson correlation was used to identify correlations between PABA recovery and intraluminal pH. A p-value <0.05 was considered statistically significant.

Results

PH-metry
Overall no significant differences were observed in the median values for twenty-four hour intragastric pH of patients that underwent PPPD and healthy control subjects (figure 2; table 1). The overall twenty-four hour intestinal pH in patients was significantly (p<0.05) higher compared to healthy control subjects.
In the postprandial periods the median intraluminal pH in patients was not different from healthy control subjects. The same holds true for the percentage of time that the pH is less than 3 or 5 respectively in the stomach or the intestinal after lunch or after dinner (figure 3).
Figure 2. Median values for daytime intragastric pH (lower panel) and intrajejunal/duodenal pH (upper panel) in patients after pylorus preserving pancreaticoduodenectomy (PPPD; n=16) and in healthy controls (n=9).

Table 1. Median twenty-four hour and postprandial (2 hours) intraluminal pH with corresponding interquartile ranges (IQR) and the intraluminal pH in the periods according to the circadian cycle of the gastric acid secretion in 16 patients after pylorus preserving pancreaticoduodenectomy and 9 healthy volunteers (controls).

<table>
<thead>
<tr>
<th>Circadian period</th>
<th>Patients Intragastric</th>
<th>Intestinal</th>
<th>Controls Intragastric</th>
<th>Intestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>1.7 (1.6-2.1)</td>
<td>6.3 (6.0-6.5) *</td>
<td>1.7 (1.5-2.0)</td>
<td>6.0 (5.9-6.1)</td>
</tr>
<tr>
<td>Postprandial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lunch</td>
<td>2.1 (1.9-2.7)</td>
<td>6.3 (5.9-6.5)</td>
<td>2.6 (1.9-3.6)</td>
<td>6.3 (5.9-6.5)</td>
</tr>
<tr>
<td>dinner</td>
<td>2.5 (1.7-4.1)</td>
<td>6.4 (5.6-6.5)</td>
<td>3.1 (2.4-3.7)</td>
<td>6.0 (5.7-6.3)</td>
</tr>
<tr>
<td>Circadian period</td>
<td>6-10 h</td>
<td>2.3 (1.6-2.8)</td>
<td>2.0 (2.0-2.9)</td>
<td>6.1 (5.9-6.2)</td>
</tr>
<tr>
<td></td>
<td>10-18 h</td>
<td>1.8 (1.4-2.0)</td>
<td>1.8 (1.6-2.1)</td>
<td>6.2 (6.0-6.4)</td>
</tr>
<tr>
<td></td>
<td>18-22 h</td>
<td>1.9 (1.6-2.0)</td>
<td>1.8 (1.6-2.5)</td>
<td>6.1 (5.8-6.2)</td>
</tr>
<tr>
<td></td>
<td>22-6 h</td>
<td>1.6 (1.3-1.9)</td>
<td>1.3 (1.2-1.7)</td>
<td>5.9 (5.9-6.1)</td>
</tr>
</tbody>
</table>

*p<0.05 compared to median intraduodenal pH in controls
When the twenty-four hour period was divided in periods corresponding with the circadian cycle of the gastric acid production, no differences were found in the intragastric and intestinal pH between patients and healthy control subjects during the daytime in the first three periods (table 1). In the nocturnal period the intestinal pH was significantly higher in patients compared to healthy control subjects. There were no significant differences in intraluminal pH profiles between the patients that underwent PPPD for ampullary carcinoma or chronic pancreatitis (table 2).

**Exocrine pancreatic function**

The mean PABA recovery of PPPD patients was 30 ± 5%. PABA recovery was abnormal in 15/16 (93%) of the patients. In 14 patients stool was collected. The mean 24 hour faecal fat excretion was 21 ± 6 g/24h. The 24h faecal fat excretion was abnormal in 8/14 (57%) of the patients. There were no significant differences in exocrine function parameters between patients that underwent PPPD for malignancy or patients that underwent PPPD for chronic pancreatitis. However, mean faecal fat excretion was more pronounced in patients with chronic pancreatitis compared to patients that underwent PPPD for ampullary carcinoma (31 ± 6 g/24h versus 13 ± 12 g/24h, respectively). No significant correlation was found between exocrine pancreatic function and intestinal (postprandial) pH in the PPPD group.
Table 2. Median twenty-four hour and postprandial (2 hours) intraluminal pH with corresponding interquartile ranges (IQR) and the intraluminal pH in the periods according to the circadian cycle of the gastric acid secretion in 16 patients after pylorus preserving pancreaticoduodenectomy for ampullary carcinoma (n=10) or chronic pancreatitis (n=6).

<table>
<thead>
<tr>
<th></th>
<th>Ampullary carcinoma</th>
<th>Chronic pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intragastric</td>
<td>Intestinal</td>
</tr>
<tr>
<td>Median 24h pH (IQR)</td>
<td>1.7 (1.6-2.1)</td>
<td>6.4 (6.1-6.4)</td>
</tr>
<tr>
<td>Median postprandial pH (IQR)</td>
<td>2.1 (1.9-2.5)</td>
<td>6.3 (5.8-6.5)</td>
</tr>
<tr>
<td>lunch</td>
<td>2.5 (2.1-3.9)</td>
<td>6.4 (5.6-6.6)</td>
</tr>
<tr>
<td>dinner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median pH in circadian periods (IQR)</td>
<td>2.3 (2.0-2.4)</td>
<td>6.3 (6.2-6.4)</td>
</tr>
<tr>
<td>6-10 h</td>
<td>1.7 (1.3-2.0)</td>
<td>6.2 (6.1-6.5)</td>
</tr>
<tr>
<td>10-18 h</td>
<td>2.0 (1.8-2.0)</td>
<td>6.3 (6.0-6.4)</td>
</tr>
<tr>
<td>18-22 h</td>
<td>1.5 (1.3-1.9)</td>
<td>6.3 (6.1-6.3)</td>
</tr>
<tr>
<td>22-6 h</td>
<td></td>
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</tr>
</tbody>
</table>

Discussion

In this study intragastric pH of patients after pylorus preserving pancreaticoduodenectomy did not significantly differ from healthy controls, whereas previously it was reported that patients with chronic pancreatitis, who frequently have an impaired exocrine pancreatic function, have a lower postprandial intragastric and intraduodenal pH. When the intraluminal pH decreases to a certain level, pancreatic enzymes (especially lipase) will be degraded and loose their effect in the nutrient digestion in the intestine. Since the intragastric and intestinal pH are not reduced after PPPD, pancreatic enzyme supplements will not run a higher risk to be inactivated compared with healthy control subjects. The median intestinal pH in patients after PPPD was not lower but even higher compared to controls. This was mainly the result of the increased intestinal pH in the nocturnal phase. During this period the intragastric pH was also higher in patients after PPPD compared to controls, although not significantly. This might be explained by either reflux of intestinal contents to the stomach as a result of a diminished pyloric function after pancreaticoduodenectomy or by a decrease in gastric acid production. A direct relation between gastric acid load and duodenal pH has been described. Still, other factors have to be taken into account. The intestinal catheter was positioned 10-15 cm distal of the pylorus. Thus, in fact intrajejunal pH in patients after pancreaticoduodenectomy is compared with the intraduodenal pH of healthy controls. Usually, in healthy volunteers the intestinal pH gradually increases going from proximal to distal. Even after resection of the duodenum the proximal jejunum, or neo-duodenum, had a higher intraluminal pH. Bile may play a role in the higher nocturnal pH of the operated patients. In healthy individuals gallbladder contraction occurs in response to food ingestion and subsequently the alkaline bile flows into the intestine and intestinal pH increases. In PPPD patients the gallbladder is resected and a hepaticojejunostomy is created. The
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reservoir function of the gallbladder is lost and therefore the hepatic bile continuously flows to the duodenum. This may result in higher nocturnal influx of bile into the intestine and subsequently a higher intestinal pH. The clinical relevance of the increase in intestinal pH in the nocturnal phase is probably limited. First, the increase in pH is only small and second, no nutrient digestion will take place in the intestine during this period.

In daytime the median overall and postprandial intestinal pH in patients after PPPD were not significantly different from healthy control subjects. This means that after PPPD the digestive function of lipase and the solubilisation of fat, which are both pH dependent, is not negatively affected because of pH. However after PPPD other factors may be present such as changes in gastric emptying or exocrine insufficiency that influence digestion and absorption of nutrients.

In the present study all patients after PPPD had an exocrine pancreatic insufficiency in terms of an impaired PABA recovery test or an increased faecal fat excretion and enzyme supplementation was indicated in order to improve nutrient digestion.

Previous studies have clearly demonstrated that addition of the proton pump inhibitor omeprazole to supplementation further reduced faecal fat excretion in patients with exocrine pancreatic insufficiency. However, even during maximal acid inhibition fat excretion did not resolve completely. Therefore other factors also play a role in the altered nutrient digestion in exocrine pancreatic insufficiency. All patients we studied after PPPD had exocrine pancreatic insufficiency. Acid inhibition should be considered in patients with high faecal fat output or weight loss despite adequate enzyme supplementation. Based on the results of the present study there is no concern that patients with PPPD are at risk for malabsorption because of lower intragastric intestinal pH. When indicated, proton pump inhibitors are preferred over H₂ receptor antagonists because in earlier reports H₂ receptor antagonists showed no additional effect in patients after PPPD.

In conclusion, the intragastric pH profiles in patients after pylorus preserving pancreaticoduodenectomy are not different from intragastric pH profiles of healthy volunteers. Intestinal pH in patients after pylorus preserving pancreaticoduodenectomy is not decreased but even increased compared to intraduodenal pH in healthy volunteers, especially in the nocturnal period. The changes in pH profiles are unlikely to negatively interfere with pancreatic enzyme supplementation and nutrient digestion.

References
Chapter 6