Resection and palliation of pancreatic and periampullary carcinoma
van Geenen, R.C.I.

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CHAPTER 7

Intragastric and intestinal pH profiles after surgical treatment for chronic pancreatitis.

R.C.I. van Geenen, MD\textsuperscript{1}, W.P. Geus, MD\textsuperscript{2,3}, C. Penning, Phd\textsuperscript{3}, E.H. Eddes, MD\textsuperscript{4}, D.J. Gouma, MD\textsuperscript{1}, A.A.M. Masclee, MD\textsuperscript{3}

From the \textsuperscript{1}Department of Surgery, Academic Medical Center, Amsterdam, \textsuperscript{2}Department of Intensive Care Leyenburg Hospital, The Hague, \textsuperscript{3}Department of Gastroenterology, Leiden University Medical Center \textsuperscript{4}Department of Surgery, Stichting Deventer Hospital

\textit{Submitted}
Abstract

Background: Chronic pancreatitis can be treated surgically by resection procedures such as duodenum preserving resection of the pancreatic head (DPRHP) or a pylorus preserving pancreaticoduodenectomy (PPPD). In patients with chronic pancreatitis postprandial intestinal and intragastric pH are significantly reduced. The effect of resection on gastrointestinal pH profiles in these patients is unknown. Therefore we have analysed gastrointestinal pH in patients after PPPD in comparison to non-operated chronic pancreatitis patients (CP).

Methods: In the period between November 1999 and January 2000, 6 patients after PPPD, 6 after DPRHP and 9 CP patients were studied. The median period between PPPD or DPRHP and measurement was 3.1 years (range 1.7-6.5 years) and 4.4 years (range 2.0-6.9). Patients underwent 24 hour ambulatory continuous intragastric and intestinal pH measurements under standardised conditions.

Results: All patients had an impaired exocrine function as measured by urinary PABA recovery and or fecal fat excretion. Median 24h intragastric pH of PPPD, DPRHP, and CP patients were 1.7 (IQR 1.6-2.9), 1.7 (IQR 1.4-2.2), and 1.6 (IQR 1.3-2.1) respectively (NS). Median 24h intestinal pH was 6.2 (IQR 6.0-6.5), 5.9 (IQR 4.3-6.6), and 5.9 (IQR 5.0-6.6), respectively (NS). There were no significant differences in median postprandial intraluminal pH in the three groups. In the circadian period from 10-18 hours, intragastric pH in the PPPD group was significantly higher than in CP group, 1.8 vs. 1.6 (p=0.05). In the circadian period from 22-06 hours intestinal pH in the PPPD group was significantly higher than in DPRHP group, 6.2 vs. 5.8 (p=0.05).

Conclusion: Median 24h intraluminal pH in patients after PPPD, DPRHP is not lower than in non-operated chronic pancreatitis patients. Therefore resection does not interfere with the food digestion by alterations in gastrointestinal pH.
Introduction
Chronic pancreatitis is a serious disease for which different therapeutic options are available based on symptoms and complications of the disease. Pain is the main indication for therapy and can be treated conservatively by pain medication, or endoscopic drainage, or surgically by neural blockade, drainage procedures or resections such as duodenum preserving resection of the head of the pancreas (DPRHP) or a pylorus preserving pancreaticoduodenectomy (PPPD).

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 intraduodenal and intragastric pH because of reduced pancreatic bicarbonate output and 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 possibly reduce (or even eliminate) its inhibitory effect on intragastric acidity which is supposed to be mediated by CCK as enterogastrone. However, after DPRHP the duodenum remains in situ and therefore the effect on gastrointestinal pH profiles may be less pronounced.

Data on the actual intragastric and intestinal pH after PPPD or DPRHP are not available but are relevant for clinical reasons. Better knowledge and insight of the consequences of resection on gastrointestinal pH may lead to improvements in pharmacological treatment of maldigestion after PPPD or DPRHP. Aim of the study was to investigate the intragastric and intestinal pH profiles in patients who underwent PPPD or DPRHP and compare the results with chronic pancreatitis with comparable impairment of pancreatic function.

Patients and Methods

Patients
In the period between November 1999 and January 2000, 6 patients (4 male, 2 female; age 33-69 years) were studied after PPPD for chronic pancreatitis, and were compared with 6 patients (5 male, 1 female; age 30-57 years) after a DPRHP for chronic pancreatitis and 9 patients (6 male, 3 female; age 28-66 years) with chronic pancreatitis, treated conservatively. The median period between PPPD and pH-metry was 3.9 years (range 1.7-6.5 years), and between DPRHP and pH-metry this was 4.4 years (range 2.0-6.9 years). All patients were operated because of severe pain and an inflammatory mass in the head of the pancreas due to chronic pancreatitis. At the Academic Medical Center PPPD procedures were performed whereas at Leiden University Medical Center DPRHP were performed.

Protocol
Patients underwent twenty-four hour ambulatory continuous intragastric and intestinal pH measurements. Medication affecting gastrointestinal motility and secretion was stopped at least three days prior to the measurements. After an overnight fast, patients came to the hospital in the
morning. In the patients after PPPD a single lumen catheter was passed transnasally into the stomach and from there it was positioned in the jejunum, 10-15 centimeters past the pylorus, under fluoroscopic control with the help of a guide wire. In patients after a DPRHP and in the non-operated group with chronic pancreatitis 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.

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 standardized 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.

**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 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.

Figure 1. Median values for daytime intragastric pH (lower panel) and intrajejunal/duodenal pH (upper panel) in patients after pylorus preserving pancreatoduodenectomy (PPPD; n=6), duodenum preserving resection of the head of the pancreas (DPRHP; n=6) and in non-operated chronic pancreatitis patients (CP; n=9).

Results
PH-metry
Overall no significant differences were observed in the median 24 hour or postprandial values for intragastric and intestinal pH of patients that underwent PPPD, DPRHP compared to chronic pancreatitis patients, or between the two types of surgery (figure 1; table 1). In the percentage of time that the pH less than 3 or 5 respectively in the stomach or the intestinal after lunch or after dinner no differences were observed between the groups (figure 2). When the twenty-four hour
period was divided in periods corresponding with the circadian cycle of the gastric acid production, no significant differences were found in the intragastric and intestinal pH between the groups apart from a significantly higher intragastric pH in the PPPD group compared to the chronic pancreatitis patients in the circadian period 10.00-18.00 hours, 1.8 versus 1.6, respectively (p=0.05) (table 1). When comparing PPPD with DPRHP patients no significant differences in intragastric or intestinal pH were observed apart from a significantly higher intestinal pH in the PPPD group in the nocturnal period (p=0.05).

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 patients after a pylorus preserving pancreatoduodenectomy (n=6) or a duodenum preserving resection of the pancreatic head (n=6) and non-operated chronic pancreatitis patients(n=9).

<table>
<thead>
<tr>
<th></th>
<th>PPPD</th>
<th>DPRHP</th>
<th>CP</th>
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<tbody>
<tr>
<td></td>
<td>Median pH (IQR)</td>
<td>Intra gastric</td>
<td>Intestinal</td>
</tr>
<tr>
<td>24h</td>
<td>1.7 (1.6-2.9)</td>
<td>6.2 (6.0-6.5)</td>
<td>1.7 (1.4-2.2)</td>
</tr>
<tr>
<td>Postprandial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lunch</td>
<td>2.6 (1.7-5.0)</td>
<td>6.3 (5.6-6.7)</td>
<td>2.3 (1.7-5.5)</td>
</tr>
<tr>
<td>Dinner</td>
<td>2.6 (1.4-4.8)</td>
<td>6.3 (3.9-6.7)</td>
<td>2.2 (1.5-3.2)</td>
</tr>
<tr>
<td>Circadian period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>06-10 h</td>
<td>2.0 (1.3-3.7)</td>
<td>6.2 (6.0-6.5)</td>
<td>2.1 (1.3-5.1)</td>
</tr>
<tr>
<td>10-18 h</td>
<td>1.8 (1.5-3.2)</td>
<td>6.1 (5.9-6.8)</td>
<td>1.8 (1.4-2.4)</td>
</tr>
<tr>
<td>18-22 h</td>
<td>1.7 (1.4-4.4)</td>
<td>6.3 (5.3-6.4)</td>
<td>1.8 (1.3-2.1)</td>
</tr>
<tr>
<td>22-06 h</td>
<td>1.6 (1.3-6.1)</td>
<td>6.2 (5.9-6.5)</td>
<td>1.5 (1.4-2.4)</td>
</tr>
</tbody>
</table>

PPPDD = pylorus preserving pancreatoduodenectomy, DPRPH = duodenum preserving resection of the head of the pancreas, CP = chronic pancreatitis. *p=0.05 compared to CP, †p=0.05 compared to DPRHP

Exocrine pancreatic function

There are no significant differences between patients after PPPD, DPRHP or chronic pancreatitis with respect to exocrine function as measured by PABA recovery or 24 hour faecal fat excretion (table 2). Only 2 patients had a normal PABA recovery test (PPPDD 1, DPRHP 1) and one other PPPD patients had a normal 24 hour faecal fat excretion. No significant correlations were found between exocrine pancreatic function and median intragastric and intestinal (postprandial) pH. A positive correlation between the PABA recovery and median intragastric pH in the circadian period from 10.00-18.00 hours was found (r=0.52, p=0.02).
Intragastric and intestinal pH profiles after pancreatic surgery

Table 2. Median PABA recovery (%) and median 24 hour faecal fat excretion (gram/24 hours) with corresponding standard errors of the mean in patients after a pylorus preserving pancreatoduodenectomy (n=6) or a duodenum preserving resection of the head of the pancreas (n=6) and non-operated chronic pancreatitis patients (n=9).

<table>
<thead>
<tr>
<th></th>
<th>PPPD</th>
<th>DPRHP</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PABA recovery (%)</td>
<td>29 ± 14</td>
<td>29 ± 6</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Abnormal PABA recovery (&lt;50%)</td>
<td>5 / 6</td>
<td>5 / 6</td>
<td>9 / 9</td>
</tr>
<tr>
<td>24 hour faecal fat excretion (grams / 24 hour)</td>
<td>31 ± 12</td>
<td>25 ± 9</td>
<td>24 ± 6</td>
</tr>
<tr>
<td>Abnormal faecal fat excretion (&gt;7 gr/24h)</td>
<td>5 / 6</td>
<td>6 / 6</td>
<td>9 / 9</td>
</tr>
</tbody>
</table>

PPPD = pylorus preserving pancreatoduodenectomy, DPRPH = duodenum preserving resection of the head of the pancreas, CP = chronic pancreatitis.

Figure 2. Box plots of the percentage of time that pH is below three for intragastric pH (Figure 2A) and below five for intrajejunal / duodenal pH (Figure 2B) for the 2 hour post-dinner period in patients after pylorus preserving pancreatoduodenectomy (PPPD; n=6), duodenum preserving resection of the head of the pancreas (DPRPH; n=6) and in non-operated chronic pancreatitis patients (CP; n=9).

Discussion
We observed that median and postprandial intragastric and intestinal pH of patients after PPPD or DPRHP are not significantly different from non-operated chronic pancreatitis patients. Patients with chronic pancreatitis are known to have a lower postprandial intragastric and intraduodenal pH⁴. Because at low intraluminal pH pancreatic enzymes (especially lipase) are degraded. This will negatively effect the nutrient digestion in the intestine. Since the intragastric and intestinal pH are not further reduced after resection, pancreatic enzyme supplements will not have a higher risk to be inactivated compared with non-operated chronic pancreatitis patients based on pH profiles.
The intragastric and intestinal postprandial pH in patients after PPPD was not lower but even higher than in the other groups, although not significantly. This finding was not expected because a reduced duodenal feedback on gastric acid secretion because of duodenal resection was likely to cause a lower intragastric pH. The somewhat higher intragastric pH might be explained by either reflux of intestinal contents to the stomach as a result of a diminished pyloric function after pancreateoduodenectomy. In the nocturnal phase the intestinal pH in PPPD patients was significantly higher compared to DPRHP patients. A direct relation between gastric acid load and duodenal pH has been described but we found no differences in intragastric pH between PPPD and DPRHP. 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 pancreateoduodenectomy is compared with the intraduodenal pH of DPRHP and chronic pancreatitis patients. Even after resection of the duodenum the proximal jejunum had a high intraluminal pH. Bile may also play a role in the higher nocturnal pH of the PPPD 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 reservoir function of the gallbladder is lost and therefore the hepatic bile continuously flows to the jejunum. This may result in higher nocturnal influx of bile into the intestine and subsequently a higher intestinal pH. After DPRHP the gall bladder remains in situ and is even enlarged. This may result in less outflow of bile during the nocturnal period and a subsequent lower nocturnal intestinal pH than in PPPD patients. 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 or DPRHP were not significantly different from non-operated chronic pancreatitis patients, except for the circadian period 10.00-18.00 hours in which the intragastric pH in PPPD patients was significantly higher. This means that after PPPD or DPRHP the digestive function of lipases and the solubilisation of fat, which are both pH dependent, are not negatively affected because of pH changes. However, one should realise that intragastric pH in chronic pancreatitis patients is already decreased. Resection procedures do not negatively affect intraluminal pH although 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 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 to nutrient digestion. There were no significant differences between the treatment groups for pancreatic insufficiency. The positive correlation between the PABA recovery and the median intragastric pH in the circadian period 10.00-18.00 hours is understandable because higher gastrointestinal pH allows better enzymatic digestion resulting in a higher PABA recovery.
In conclusion, the intragastric and intestinal pH profiles in patients after pylorus preserving pancreaticoduodenectomy or duodenum preserving resection of the pancreatic head are not significantly different non-operated chronic pancreatitis patients and have a comparable degree of exocrine insufficiency. Surgical treatment of chronic pancreatitis does not negatively interfere with intraluminal pH and subsequent pancreatic enzyme activity and nutrient digestion.

References


