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Intraluminal gastric pH in chronic pancreatitis

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Abstract

The aim of this study was to assess the circadian variations of intragastric pH in 28 inpatients with chronic pancreatitis (mean (SD) age 46·8 (12·4) years) and in 14 controls (45·4 (9·8)). pH Metry was performed using a monocrystalline antimony electrode placed in the body of the stomach under fluoroscopic control and connected up to a recorder (MKII Digitrapper, Synectics). The evaluation parameters, expressed as median and interquartile range, were: total period, postprandial periods (P1 and P2), interdigestive, and nocturnal phases. Patients with chronic pancreatitis were subdivided into three groups on the basis of severity of exocrine pancreatic insufficiency (secretin-caerulein test: lipase output at 60–90 min) – that is, those with severe insufficiency (chronic pancreatitis-SI: 13 patients, lipase output <10% normal values and pancreolauryl test <20%), those with only mild insufficiency (chronic pancreatitis-MI: seven patients), and those with normal secretion (chronic pancreatitis-NF: eight patients). The chronic pancreatitis-SI patients present significantly greater gastric acidification in the postprandial periods compared with controls (P1: $p<0·001$; P2: $p<0·01$), and with chronic pancreatitis-MI plus chronic pancreatitis-NF subjects (P1: $p<0·01$; P2: $p<0·05$), taken together. In conclusion, gastric acidity, exocrine pancreatic insufficiency, and impaired digestion are closely related during the course of chronic pancreatitis.

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Keywords: pancreatic insufficiency, chronic pancreatitis, intraluminal gastric pH.

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The behaviour of gastric acid secretory function in the course of chronic pancreatitis and the correlation between gastric acid secretion and the presence or degree of exocrine pancreatic insufficiency, or both and impaired digestion are still highly controversial issues.

Whereas certain investigators,[1–3] in studies of gastric aspirate after pentagastrin stimulation, have detected acid hypersecretion in chronic pancreatitis patients both in basal conditions and after stimulation, others, measuring acid output after a meal[4] or analysing serum pepsinogen I concentrations,[5] have reached diametrically opposite conclusions.

While the study of gastric acid secretion after hormonal stimulation with an exogenous secretagogue clearly does not constitute a physiological approach to the problem, the analysis of gastric aspirates collected over brief postprandial periods provides very precise information, though, unfortunately, it entails a very complex procedure and as such is particularly prone to errors of execution.[6]

Twenty four hour pH metry, however, permits evaluation, in physiological conditions, of the circadian pattern of the gastric intraluminal gastric pH, which is closely correlated with changes in acid secretion.[7–10]

The aim of this study was to measure 24 hour intragastric pH in subjects suffering from chronic pancreatitis with and without severe exocrine pancreatic insufficiency and in the presence or absence of impaired digestion.

Patients and methods

The study was conducted on 28 hospital inpatients (26 males, two females; mean (SD) age: 46·8 (12·4) years) suffering from chronic pancreatitis. The diagnosis of chronic pancreatitis was based on clinical parameters and laboratory and instrumental tests (ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography, secretin-caerulein test).

Twenty three of 28 patients presented pancreatic calcifications at ultrasonography. The mean (SD) alcohol intake was 105·8 (63·0) g ethanol/day (range: 40–250 g/day). None of the patients had had gastrointestinal, pancreatic or biliary tract surgery.

The control group comprised 14 healthy subjects (12 males, two females; mean (SD) age: 45·5 (9·8) years) with no evidence of gastroenterological disease.

All types of treatment with pancreatic enzymes, H_2 antagonists, prokinetic drugs or antacids was stopped at least five days before the study, during which all subjects were receiving a standardised hospital diet (2000 kcal/day; carbohydrates 65%; proteins 20%; fat 15%).

TWENTY FOUR HOUR INTRAGASTRIC pH METRY

All subjects examined were submitted to 24 hour intragastric pH metry using monocrystalline antimony electrodes (Monocrystant mod 0011) positioned in the gastric corpus 10 cm below the lower oesophageal sphincter with fluoroscopic control at the beginning and at the end of the examination. The exploring antimony electrode was carefully calibrated at the beginning and at the end of each examination using commercially available standard buffer solutions (pH 1·07 and pH 7·01, respectively; Synectics, Sweden). The electrode drift at the end of each test was negligible – that is,

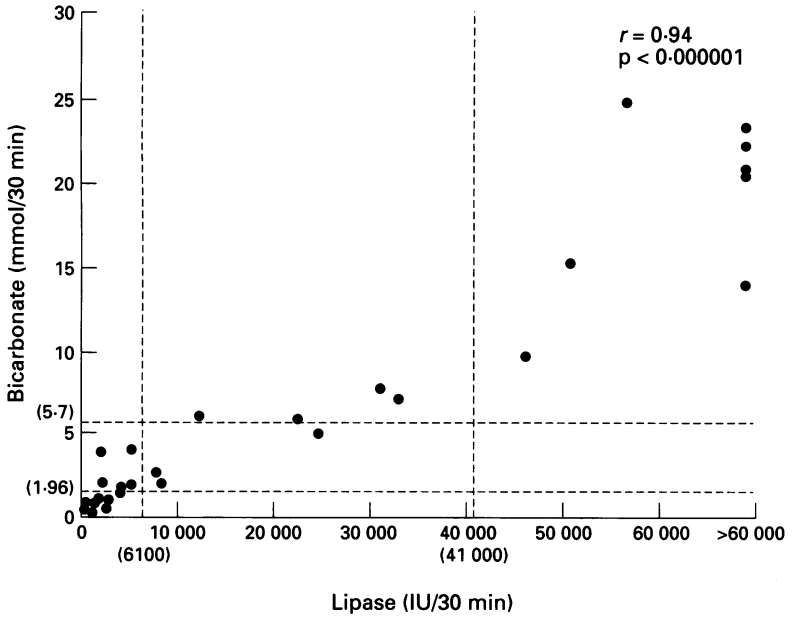

Figure 1: Lipase and bicarbonate secretion values (output/30 min) during secretin-caerulein test.

less than 0·1 pH unit. An Ag-AgCl reference skin electrode was placed on the upper thorax. The recording system used consisted of a twin channel portable digital appliance for recording pH (Digitrapper MK II, Synectics, Sweden) with a storage capacity of 24 hours and preset four second measurement intervals.

As evaluation parameters we considered the median and interquartile intervals of the total pH metric measurement period (24 hours), the two postprandial periods corresponding to the main meals (P1 and P2), the two interdigestive phases (ID1 and ID2, respectively), and the nocturnal period (N).

The patients suffering from chronic pancreatitis were then submitted, on different days, to the secretin-caerulein test for evaluation of exocrine pancreatic insufficiency and to the pancreolauryl test for proof of impaired digestion.

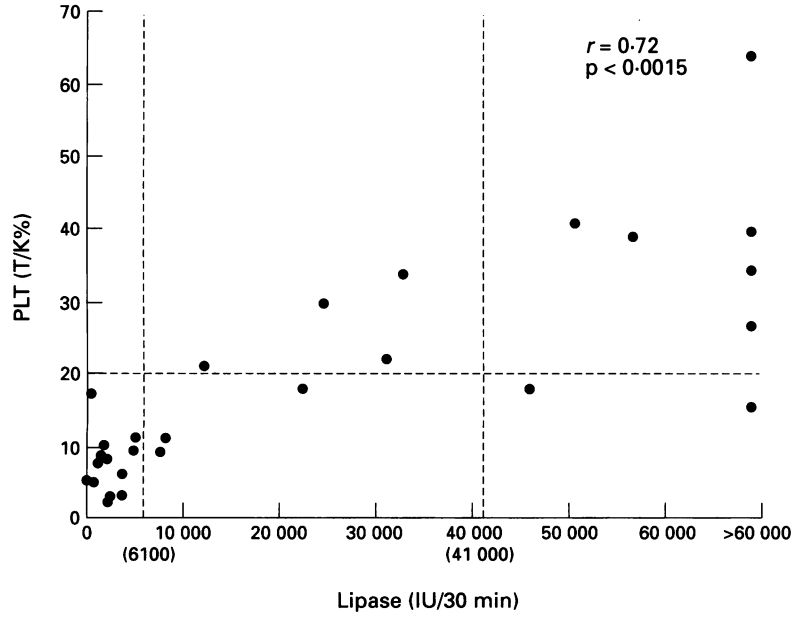

Figure 2: Individual pancreolauryl test (PLT) results plotted against lipase secretion (output/30 min) in chronic pancreatitis patients.

SECRETIN-CAERULEIN TEST

The secretin-caerulein test (secretin: Kabi Diagnostica, Studswik, Sweden; caerulein: Farmitalia-C Erba, Milan, Italy) was performed in all the chronic pancreatitis patients as described elsewhere,[11 12] by intravenous infusion of secretin (0·5 CU/kg/h) plus caerulein (75 ng/kg/h) for 120 minutes. This dose provides a maximal or near maximal stimulation of pancreatic secretion and therefore gives information on the exocrine pancreatic capacity.[11–13]

The indices used for pancreatic exocrine function were duodenal lipase output and bicarbonate measured over 60–90 minutes. Lipase was assayed by automatic titration (TTT80 Radiometer) according to Sarles *et al.*[14] Bicarbonate was measured by back titration.

Pancreatic exocrine function was classified according to Cavallini *et al*[15]: (a) normal function (NF): lipase output above 41 000 IU/30 min; (b) moderate insufficiency (MI): lipase output between 41 000 and 6100 IU/30 min; (c) severe insufficiency (SI): lipase output below 6100 IU/30 min.

PANCREATIC IMPAIRED DIGESTION

Pancreatic impaired digestion was confirmed by means of the pancreolauryl test (Temmler-Werke, Marburg, Germany) performed as already described.[15] After overnight fasting, all the subjects were given, together with a continental breakfast, 348·5 mg (two blue capsules) of fluorescein dilaurate and, two days later, 188·14 mg (one red capsule) of sodium fluorescein. Over the 10 hours after administration, the patients drank 1·5 litres of water or unsweetened tea. During this period of time, all the urine for the fluorescein determination was collected and stored at −20°C until assay. The relative percentage of urinary excretion of fluorescein (pancreolauryl test – T/L%; T=excretion of dye from fluorescein dilaurate; K=excretion of dye from sodium fluorescein) was calculated.[16] Twenty per cent was considered as the cut off limit for urinary T/K. Below this value the pancreolauryl test was regarded as abnormal, as we previously reported[17]; the 20% cut off yields better overall accuracy than the 30% value in the diagnosis of pancreatic exocrine insufficiency.[17]

STATISTICAL ANALYSIS

Data were analysed statistically using the Kruskall-Wallis test, the Mann-Whitney U test, and calculation of Spearman's coefficient of correlation *r*.

Results

Figure 1 gives the values for lipase and bicarbonate secretion during the secretin-caerulein test.

Severe enzymatic insufficiency (SI) was seen in 13 patients with chronic pancreatitis, moderate insufficiency (MI) in seven, and normal lipase and bicarbonate secretion (NF)

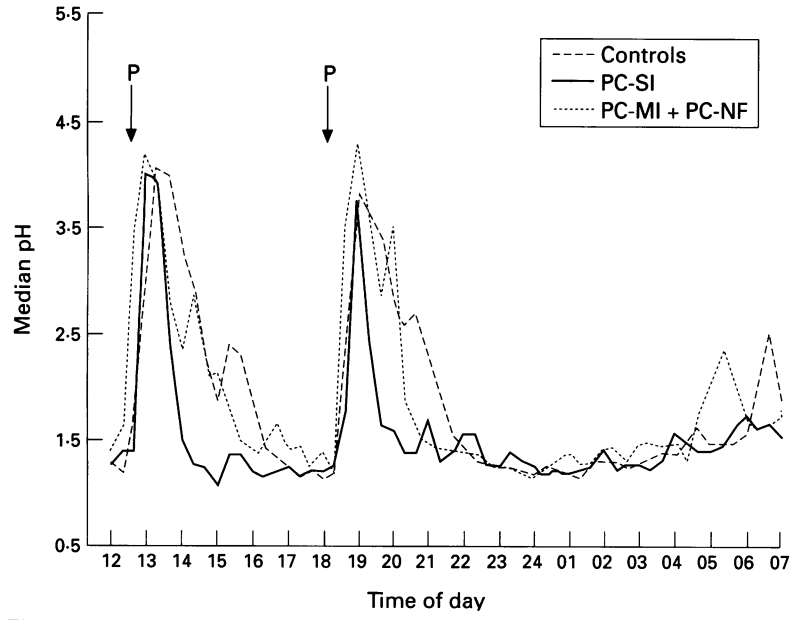

Figure 3: Twenty four hour pH profiles for chronic pancreatitis patients with (CP-SI) and without (CP-MI+CP-NF) severe exocrine pancreatic insufficiency in comparison with control subjects.

in eight. Because of the small size of the sample and the similar patterns recorded, these last two subgroups of patients were also pooled together under the heading chronic pancreatitis-MI+chronic pancreatitis-NF.

Bicarbonate secretion was curtailed in all 13 chronic pancreatitis patients with SI (a severe reduction was found in eight and a moderate reduction in five) and in three of the chronic pancreatitis patients with MI and NF (moderate reduction).

There is a close correlation between lipase and bicarbonate secretion (r=0·94; p<0·000001).

The pancreolauryl test proved abnormal in all chronic pancreatitis patients with SI (Fig 2).

Figure 3 shows the pH profile for controls, chronic pancreatitis patients with severe insufficiency (chronic pancreatitis-SI), chronic pancreatitis patients with moderate insufficiency (chronic pancreatitis-MI), and those with normal function (chronic pancreatitis-NF). In the postprandial periods there is an earlier drop in postprandial pH, the more severe the pancreatic insufficiency. In fact, when pH showed peak values in the postprandial periods P1 and P2 (Fig 4), it proved significantly lower in the chronic pancreatitis-SI group compared with the control group (P1: p<0·001; P2: p<0·01) and with the chronic pancreatitis-MI plus chronic pancreatitis-NF groups, taken together (P1: p<0·01; P2: p<0·05), but not when the chronic pancreatitis-MI and chronic pancreatitis-NF groups were considered separately (Fig 4). The lack of statistical significance in this last case is probably because of the very limited numbers of patients in the two groups (seven and eight patients, respectively).

Though the median pH values in the chronic pancreatitis-MI and chronic pancreatitis-NF groups were lower than that in the control group, the difference was not statistically significant.

In the same postprandial periods, the gastric mucosa of the chronic pancreatitis-SI patients was exposed for a significantly longer time period to pH values of 2 or less (Fig 5) compared with controls. Here again, a different trend was seen when chronic pancreatitis-MI and chronic pancreatitis-NF were considered separately in comparison with controls, but the differences failed to prove significant.

A significant correlation was seen, moreover, between median postprandial (P1 and P2) pH values and lipase secretion (Fig 6) (r=0·52, p<0·01). Similar correlations were also found between median postprandial pH and both bicarbonate secretion (r=0·42, p<0·05) and pancreolauryl test (r=0·43, p<0·05) (data not shown).

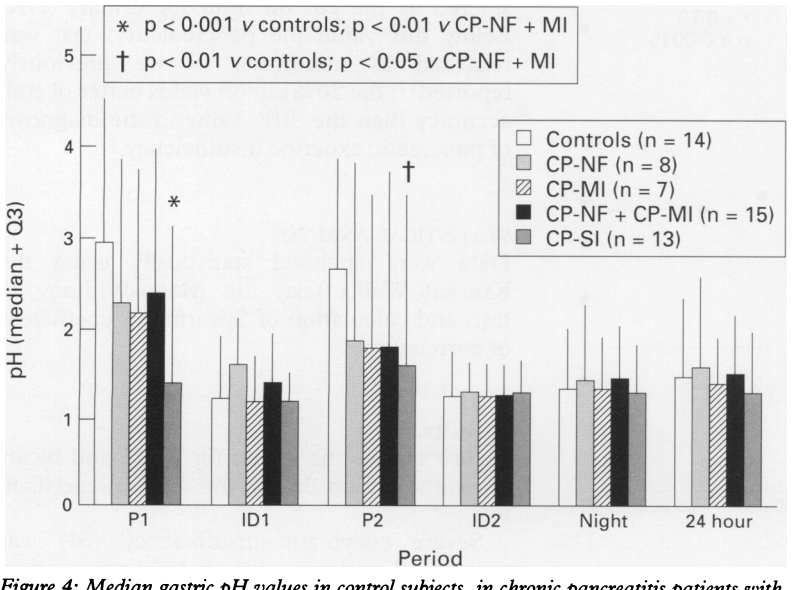

Figure 4: Median gastric pH values in control subjects, in chronic pancreatitis patients with severe (CP-SI) or moderate (CP-MI) exocrine pancreatic insufficiency and in those with normal function (CP-NF).

Discussion

The results of this study show that after a standard meal patients with chronic pancreatitis and severe exocrine pancreatic insufficiency present a longer period of gastric acid exposure, compared with patients with moderate pancreatic insufficiency or normal pancreatic function.

In this last group, however, there is a tendency towards greater postprandial acidification. Our results are in agreement with those reported by Saunders[18] and Piubello[2] regarding an increase in gastric acidity (basal and after hormonal stimulation) in chronic pancreatitis patients with exocrine pancreatic insufficiency, but they are at variance with the data reported by Reagan *et al.*[4]

This last study reported that, in patients with chronic pancreatitis, postprandial acid secretion was reduced and associated with increased gastrinaemia. These data might mean that the patients studied by Reagan *et al*[4] were suffering from a possibly alcohol induced chronic atrophic gastritis, though we cannot rule out the possibility that the actual

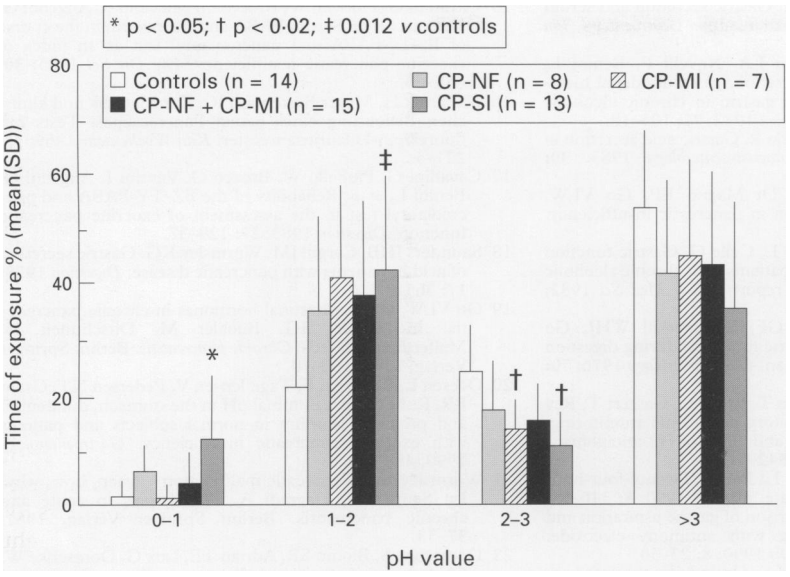

Figure 5: Mean gastric acid exposure values by pH classes in postprandial periods in control subjects and in chronic pancreatitis patients with severe (CP-SI) or moderate (CP-MI) exocrine pancreatic insufficiency and in those with normal function (CP-NF).

composition of the meals used by Reagan (more lipids and proteins) and by our group (more carbohydrates) may have contributed to the different acid and hormonal responses.[19] Systematic histological and endoscopic data at a gastric level, however, are lacking both in our patients and in those studied by Reagan *et al.*

The low postprandial pH values we detected in chronic pancreatitis patients are consistent, albeit only partially, with the results obtained in a study on duodenal pH patterns in subjects with chronic pancreatitis and severe pancreatic insufficiency.[20] It has been shown, in fact, that in these patients, 70–80 minutes after ingestion of a liquid meal (Lundh meal), the pH of the duodenal bulb was exposed for roughly 10 minutes, to a significantly greater acidification than duodenal bulb pH in control subjects. A similar, though non-significant trend was also seen in the fasting periods and two hours after the meal.

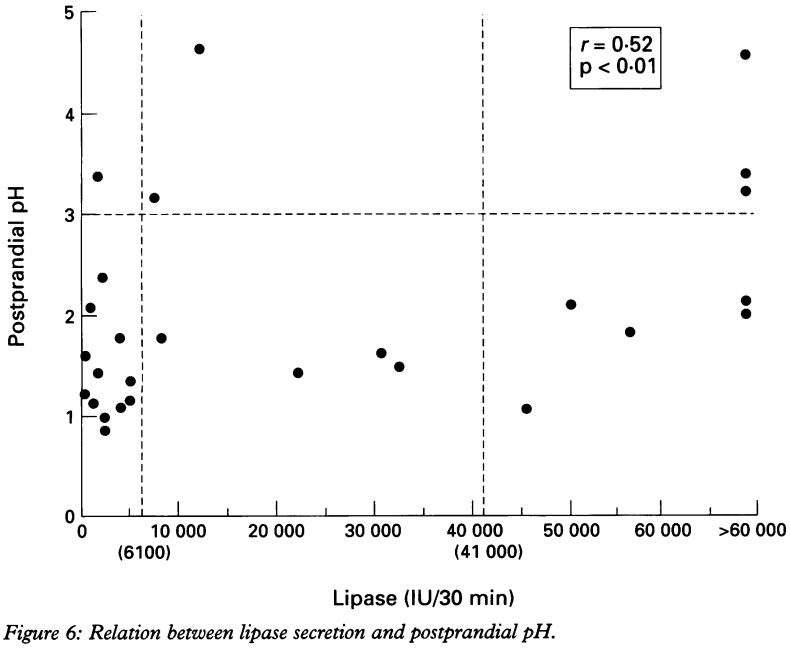

Figure 6: Relation between lipase secretion and postprandial pH.

In a joint assessment of our data and those reported by Ovesen,[20] it can be seen that, in the presence of severe pancreatic insufficiency, the greater and longer lasting postprandial gastric acidification may lead to a greater acidification of the duodenal areas most exposed to the gastric acid load.

On the other hand, as the severe lipase insufficiency (at least in our patients) is associated in most cases (62%) with a noticeable reduction in bicarbonate secretion, the poor intraluminal diffusion of bicarbonate may contribute towards increasing the acidity of the duodenojejunal milieu.

The mechanisms underlying the greater gastric acidification in the presence of exocrine pancreatic insufficiency are still only poorly known. The finding of an abnormal pancreolauryl test in our patients with severe enzyme secretion insufficiency means that these patients present a severe lipid impaired digestion, and this last factor has been described as possibly being responsible for an increase or prolongation of the acid secretory response, or both particularly in the postprandial period, caused by the lack of the inhibition of hydrochloric acid normally induced by the presence of mono and diglycerides in the duodenojejunal lumen.[21]

Another mechanism can also be considered consisting of deficient secretion of trypsinogen, the non-active fragment of which may exert an inhibitory effect on gastric hydrochloric acid.

Intestinal hormones, for example, enterogastrone like substances, may also play a part in promoting greater gastric acidity. As far as gastric inhibitory peptide is concerned, it is known that its secretion by the proximal jejunum and duodenum is stimulated by digested substances contained in the lumen and in particular by simple sugars such as glucose.[22 23]

In patients with chronic pancreatitis and pancreatic insufficiency the existence has been shown of a reduced gastric inhibitory peptide response after a test meal, which is reversible after oral administration of pancreatic enzymes.[24] In these patients, there may be a lack of inhibition of gastric secretion with persistence of hyperacidity resulting from a defective release of gastric inhibitory peptide.

The existence of some kind of relation between postprandial gastric acid response and insufficiency of digestive phenomena would seem to be confirmed in this study by the finding that postprandial pH correlates well not only with lipase and bicarbonate secretion, but also with the pancreolauryl test values.

In conclusion, the data obtained in this study suggest that patients with chronic pancreatitis and severe exocrine insufficiency present a greater and longer lasting postprandial gastric acidification. This greater degree of gastric acidity may lead in turn to periods of duodenal hyperacidity and aggravate the state of impaired digestion, as well as predisposing to peptic type lesions. These findings must be considered when regarding the possible use of gastric antisecretory agents and the choice of enzyme replacement preparations.

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