A Comparative Study on Gastric Emptying and Secretory Status in the Early Postoperative Period after Truncal Vagotomy with Two Pyloroplasty Variants Performed for Peptic Ulcer Disease II. Heineke-Mikulicz Pyloroplasty and Comparison with the Cassimally Routine

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In 14 peptic ulcer patients undergoing truncal vagotomy with Heineke-Mikulicz pyloroplasty (VTP-HM), gastric emptying of a radiolabeled solid meal, gastric acid secretion and gastrin release was examined within a median of 14 days (range: 10 to 63 days) following the operation, and compared with the results obtained in 14 patients subjected to vagotomy and Cassimally pyloroplasty (VTP-Cas).

VTP-HM markedly disturbed gastric emptying in 10 out of 14 patients (71%), four of which (28%) had extremely rapid, and six (43%) exhibited abnormally delayed gastric emptying. Due to a wide inter-subject variability, no significant differences between VTP-HM and VTP-Cas were found for any of the gastric emptying parameters considered. The basal acid output was significantly lower after VTP-Cas than VTP-HM: 2.4 ± 0.8 vs 5.8 ± 1.0mmol·h⁻¹, (p<0.02). The difference in pentagastrin-stimulated gastric acid secretion: 9.4 ± 1.4 vs 12.0 ± 1.8 mmol·h⁻¹ for VTP-Cas vs VTP-HM, respectively, was not statistically significant. Higher fasting serum gastrin concentration (102.0 ± 21.1 vs 63.3 ± 8.5 ng·l⁻¹), and greater postprandial gastrin release (AUC0-120: 16690 ± 2648 vs 10654 ± 1283 ng·l⁻¹·min) were observed after VTP-HM than after VTP-Cas. The respective differences did not, however, reach the level of statistical significance. The possible clinical relevance of the differences between the two pyloroplasty procedures with respect to their effect on gastric evacuatory and secretory functions is discussed.

(Key Words: Cassimally pyloroplasty, Gastric acid secretion, Gastric emptying, Gastrin, Heineke-Mikulicz pyloroplasty)

INTRODUCTION

It is known from clinical experience that vagal denervation of the stomach together with pyloroplasty allows patients to overcome their peptic ulcer problems. Unfortunately, in a number of subjects new problems of inappropriate gastric emptying may arise postoperatively which, in general, can be categorized into two contrasting types: the dumping syndrome and gastric stasis. In fact, examinations by MacGregor et al. (23) and Mayer et al. (24) indicated extreme inter-individual variations of solid gastric emptying after truncal vagotomy and pyloroplasty. Wittebol et al. (31) proved in their recent study that a significant correlation exists between postoperative postprandial symptoms and the gastric emptying pattern of semisolid and solid meals as determined using a non-invasive quantitative radioisotopic technique.

The conflicting results of previous studies intended to measure gastric emptying after truncal vagotomy with pyloroplasty appear due to major differences among them with respect to the methods of measuring gastric emptying.
time elapsing between surgery and the gastric emptying examination, and the reference group of subjects assumed to have normal gastric emptying (1, 2, 5, 6, 12, 26, 30). Moreover, in a majority of these studies no mention was made of the type of pyloroplasty performed. It is worth noting that Davies et al. (4) demonstrated in their study that even the type of drainage procedure may affect the gastric emptying postoperatively.

In the present study we evaluated the effect of truncal vagotomy with Heineke-Mikulicz pyloroplasty (VTP-HM) on gastric emptying of a solid meal, gastric acid secretion and gastrin release. The examinations were performed during the early postoperative period, i.e., within 9 weeks after the surgery. This approach revealed the direct effect of a stomach operation on gastric emptying before adaptive changes developed. The results of this work are compared with those of a concomitant study on the effect vagotomy with Cassimally pyloroplasty (VTP-Cas) on gastric evacuatory and secretory functions (cf. ref. 22.).

PATIENTS AND METHODS

Truncal vagotomy with Heineke-Mikulicz pyloroplasty (11) was performed for peptic ulcer disease on 14 patients, 13 men and one woman, with a mean age of 43.4 years (range; 24 to 80 years). In endoscopy and/or surgery, the ulcer was found to be localized in the duodenal bulb in eight patients, and in the pylorus in four, and a type I gastric ulcer according to the classification by Johnson (13) was diagnosed in two patients. The median disease duration was 5 years (range: 0 to 30 years). Six patients were operated on electively because of a recent history of upper gastrointestinal tract hemorrhage which was stopped by conservative pharmacological treatment. Eight subjects underwent emergency surgery because of perforated ulcers. Other organic diseases were excluded in all patients on the basis of questioning concerning history, physical examination and routine laboratory tests. In the patients with gastric ulcers, malignancy was ruled out by histopathological examination of multiple biopsies performed during endoscopy.

Preoperative measurement of gastric emptying was performed in six subjects at a median interval of 9 days (range; 4 to 27 days before the surgery). All 14 patients underwent postoperative gastric emptying examinations at a median interval of 14 days (range: 10 to 63 days) after VTP-HM. In addition, pre- and postoperative determinations of the basal and pentagastrin-stimulated gastric acid output were performed in four patients, whereas 10 subjects were examined postoperatively only. In four patients both the pre- and postoperative and in eight subjects only postoperative measurement of the basal and meal-stimulated gastrin release was performed. The postoperative examination of gastric acid and gastrin secretion took place within two months after the surgery. The patients received no medication throughout the examination period. The study was performed in line with the Helsinki Declaration and written informed consent was obtained from every patient.

Measurement of gastric emptying

The patients refrained from smoking and fasted overnight before the examination. As described previously (14, 15), a standard test meal consisting of $^{99m}$Tc-labeled scrambled eggs (16–18), white bread and 250 ml of skimmed milk was given to the patients in the morning. The time needed to consume the meal did not exceed 5 min. With 7.4 MBq of $^{99m}$Tc activity used in each examination, the estimated whole body irradiation amounted to $3.6 \times 10^{-5}$ Gy. Data acquisition started immediately after meal completion. Thirty 2-min counts were registered with a patient sitting immobile in a comfortable armchair in front of a gamma camera coupled on-line with a computer (MB 9100, Gamma Müvek Budapest, Hungary). A parallel-hole high-resolution collimator was used. The analyzer was set at the 140 keV photopeak with a 20% energy window width. Quantitative analysis of the stored data was performed as follows. The whole-stomach region of interest (ROI) was defined by an edge-finding program. Time-activity curves from the gastric ROI were corrected for physical decay of the isotope and normalized for the fraction of activity remaining within the stomach (considering the peak activity frame to be 1.0). Taking into account previous investigations (19, 20), background correction was omitted as negligible. Correction for spatial movement of the tracer within the stomach was assured by
the experimental design considering each subject to be his own control. As described previously (16–18), the normalized gastric emptying curves were fitted with a power-exponential function (7) in order to derive the gastric half emptying time, T1/2, curve shape parameter S, and the slope of the curve K (17, 18). Moreover, the gastric emptying index, Ix, was computed from the unfitted gastric emptying curves (14, 18). In an earlier study we provided convincing evidence of the short- and long-term reproducibility of this method of measuring gastric emptying (17). In examinations performed under the experimental conditions described on 41 healthy subjects (29 men and women, mean age; 31.4 years, range: 18 to 48 years), normal values of the gastric emptying parameters were established as follows: T1/2 = 81.5 ± 4.5 min, S = 1.010 ± 0.038, K = 9.54 ± 0.63 min⁻¹·10⁻³, and Ix = 1.94 ± 0.13 min⁻¹·10⁻² (mean ± SEM values), and these results have been used in this paper as a reference basis for comparisons with patients’ data. A patient was considered to show abnormal gastric emptying if any of the gastric emptying parameters was outside the two-tailed 95% confidence limit established in normal subjects, i.e., outside the mean ± 2 standard deviations (SD) range (10).

Gastric acid and gastrin secretion tests
The basal and pentagastrin-stimulated (6 μg·kg⁻¹·body mass s.c.) gastric acid output was assessed according to the routine procedure described by Konturek (21). On a different day, two samples of venous blood were taken 15 and 5 min before consumption of a test meal to assess gastrinemia in the fasting state. Then the patients consumed a test meal consisting of two hard boiled eggs, 50g of white bread and 250ml of sweetened fruit juice (29) and venous blood samples were collected 5, 15, 30, 40, 60, and 120 min postprandially. The meal was prepared in a separate room and was not presented to the subjects until it was time for application of the meal stimulus. Serum was separated by centrifugation and kept frozen at −20°C until assayed. Serum gastrin concentrations were determined radioimmunologically using a commercially available kit (Gastrin Kit, code 10994, Biodata, Italy). The sensitivity of the kit was not lower than 10ng·l⁻¹·gastrin. Intra- and inter-assay coefficients of variation established in our laboratory for this assay were 5.0 and 7.1%, respectively. The postprandial gastrin output was expressed as the integrated response by calculating the area under the gastrin curve (AUCO–120) by the trapezium-method.

Statistical methods
Statistical analysis was performed using the paired and unpaired Wilcoxon signed rank tests. The p < 0.05 level (two-tailed) was considered to be significant. Results shown in the paper are means ± SEM or medians and ranges, depending on the distribution of numerical data.

RESULTS
Effect of VTP-HM on gastric emptying, gastric acid and gastrin secretion
The power-exponential function provided a very good fit of the experimental gastric emptying data in all but two patients in whom almost all of the radiolabeled meal was retained within the stomach throughout the examination postoperatively. The assumption that T1/2 equaled 500 min and K equaled 0 enabled inclusion of these two cases in the analysis with the non-parametric Wilcoxon test. No valid assumptions could, however, be made with respect to the shape parameter S, and therefore these data were omitted from analysis.

A limited number of paired, i.e. taken before and after the surgery, measurements of gastric emptying did not permit any valid statistical comparisons. Nevertheless a glance at the individual changes of parameters reflecting either the gastric emptying speed (T1/2 and K) or the gastric emptying pattern (S) indicated the most variable outcome for VTP-HM, which was reflected by strongly delayed gastric emptying in some patients and very rapid gastric evacuation in the others (Fig. 1 A, B, and C). As shown in Table 1, postoperative gastric emptying in patients subjected to VTP-HM seemingly did not differ from healthy controls. A closer inspection of individual postoperative gastric emptying data (Fig. 2.) revealed, however, that in as many as 10 out of 14 patients (71%) gastric emptying was apparently abnormal, but in six of these 10 subjects (43%) a marked delay in gastric emptying occurred (T1/2 exceeded the limit of mean T1/2 ± 2 SD in healthy controls), and in four subjects (28%),
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Fig. 1—panel A

Fig. 1—panel B
Fig. 1 Individual changes in gastric half emptying time, $T_{1/2}$ (panel A), curve shape parameter, $S$ (panel B), and slope of gastric emptying curve, $K$ (panel C) observed in patients undergoing vagotomy and Heineke-Mikulicz pyloroplasty: $\circ =$ duodenal, $\triangle =$ pyloric and $\Box =$ gastric ulcer before surgery, whereas the corresponding symbols: $\bullet$, $\triangle$ and $\Box$, reflect the postoperative situation; the horizontal bars are the medians. For comparison, the ranges: mean $\pm$ 1 SD (---) and mean $\pm$ 2 SD (-----) of $T_{1/2}$, $S$, and $K$ variability established in 41 healthy controls are also plotted.
very rapid gastric evacuation was found (T1/2 at the border of or below the mean T1/2 ± 2 SD in healthy subjects). This precipitous gastric emptying was also reflected by abnormally high values of the slope of the gastric emptying curves (Fig. 2).

On the basis of four paired pre- and postoperative examinations of gastric acid output, decreases in the basal acid output from 2.7 ± 0.8 to 2.2 ± 0.9 mmol·h⁻¹, and in the pentagastrin-stimulated acid output from 16.8 ± 1.8 to 7.2 ± 2.8 mmol·h⁻¹ after VTP-HM were noted. Similarly, only a limited evaluation of VTP-HM-induced changes in gastrin release could be inferred from the results of the four paired measurements available. Nevertheless, these data indicated a strong increase either in basal serum gastrin concentration (54.4 ± 4.4 ng·l⁻¹ before vs 164.4 ± 45.4 ng·l⁻¹ after VTP-HM) or in meal-stimulated gastrin release (AUC₀₋₄₅₀: 8455 ± 516 ng·l⁻¹·min before vs 25730 ± 4568 ng·l⁻¹·min after VTP-HM) after the surgery.

**Comparison of the VTP-HM and VTP-Cas procedures with respect to their effect on gastric emptying, as well as gastric acid and gastrin secretion**

Despite an obvious difference in the medians of the gastric emptying parameters after the two surgical procedures, suggesting that slower gastric emptying occurred after VTP-Cas than after VTP-HM (Fig. 2.), wide interindividual variations in the postoperative measurements prevented this observation from being proven statistically (Table 1).

Higher fasting serum gastrin concentration and greater postprandial gastrin release, as well as higher basal and pentagastrin-stimulated gastric acid output were found after surgery in the VTP-HM patients than in the VTP-Cas patients, but the difference reached the level of
Gastric Emptying, Acid and Gastrin Output after Cassimally VTP—475

Table 1 Postoperative gastric emptying (GE) data patients subjected to vagotomy and Heineke-Mikulicz pyloroplasty (VTP-HM) in comparison with healthy controls and those undergoing vagotomy and Cassimally pyloroplasty (VTP-Cas) (cf. ref. 22.)

<table>
<thead>
<tr>
<th>GE Parameter</th>
<th>VTP-HM patients</th>
<th>Healthy controls</th>
<th>VTP-Cas patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2³</td>
<td>76 (18–500)</td>
<td>76 (26–167)</td>
<td>116 (22–935)</td>
</tr>
<tr>
<td>(n=14)</td>
<td>(n=41)</td>
<td>(n=14)</td>
<td></td>
</tr>
<tr>
<td>s⁴</td>
<td>1.05 (0.50–2.03)</td>
<td>1.03 (0.61–1.65)</td>
<td>0.82 (0.26–3.46)</td>
</tr>
<tr>
<td>(n=12)</td>
<td>(n=41)</td>
<td>(n=13)</td>
<td></td>
</tr>
<tr>
<td>K⁵</td>
<td>9.80 (0–32.32)</td>
<td>9.09 (3.72–28.66)</td>
<td>5.70 (0–33.71)</td>
</tr>
<tr>
<td>(min⁻¹10⁻⁵)</td>
<td>(n=14)</td>
<td>(n=41)</td>
<td>(n=14)</td>
</tr>
<tr>
<td>Ix⁶</td>
<td>2.48 ± 0.56</td>
<td>1.94 ± 0.15</td>
<td>1.76 ± 0.44</td>
</tr>
<tr>
<td>(n=14)</td>
<td>(n=41)</td>
<td>(n=14)</td>
<td></td>
</tr>
</tbody>
</table>

a) Median and range; b) Mean ± SEM
T1/2 = gastric half emptying time; S = curve shape parameter; K = slope of a gastric emptying curve; Ix = gastric emptying index. No statistically significant differences were found between any of the groups compared.

Table 2 Comparison of postoperative data with regard to gastrin release and gastric acid secretion in patients subjected to vagotomy and Cassimally pyloroplasty (VTP-Cas) and those undergoing vagotomy and Heineke-Mikulicz pyloroplasty (VTP-HM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VTP-Cas patients</th>
<th>VTP-HM patients</th>
<th>Significant differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum gastrin (ng/l⁻¹)</td>
<td>65.3 ± 8.3</td>
<td>102.0 ± 21.1</td>
<td>NS</td>
</tr>
<tr>
<td>(n=13)</td>
<td>(n=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprandial gastrin, AUC₀⁻₁₂₀ (ng/l⁻¹ min)</td>
<td>10654 ± 1283</td>
<td>16690 ± 2648</td>
<td>NS</td>
</tr>
<tr>
<td>(n=13)</td>
<td>(n=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal acid output (mmol/h⁻¹)</td>
<td>2.4 ± 0.8</td>
<td>5.8 ± 1.0</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>(n=11)</td>
<td>(n=14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal acid output (mmol/h⁻¹)</td>
<td>9.4 ± 1.4</td>
<td>12.0 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>(n=11)</td>
<td>(n=14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SEM; AUC₀⁻₁₂₀ = area under the gastrin curve

statistical significance only in the case of the basal acid output (Table 2.).

DISCUSSION

Experimental surgery based on animal studies offers a unique opportunity to perform programed stage-by-stage operations. Yamagishi and Debas (33) demonstrated in dogs that Heineke-Mikulicz pyloroplasty alone caused a minor acceleration of gastric emptying of liquids but did not affect the emptying of a solid meal. The subsequent addition of vagotomy to Heineke-Mikulicz pyloroplasty further accelerated the gastric emptying of liquids, but had no effect on the gastric evacuation of solids (33). On the other hand, vagotomy alone significantly inhibited gastric emptying of both the liquid and solid phases of a meal (33). An attempt to extrapolate the results of such animal studies as cited to human clinical practice is, however, hindered not only by possible interspecies differences but also by the fact that patients are operated on for a specific underlying disease such as peptic ulcer disease which per se may disturb gastric emptying, whereas experimental surgery is performed on healthy animals.

Cowley et al (3) found that gastric emptying of the liquid phase of a meal was significantly delayed within one to four weeks after VTP-
HM, while within 1 to 4 months postoperatively a trend towards a normalization of the gastric evacuation of liquids was observed. Examinations performed in the late postoperative period revealed a speed-up of gastric emptying of liquids after VTP-HM (9, 32), a finding which was in agreement with the observations derived from experimental surgery (33).

Gastric emptying of a solid meal after VTP-HM was examined previously in two studies only. Calabuig et al (2) did not find any significant difference in the gastric emptying of solids between VTP-HM patients examined at a mean of 35 ± 17 months postoperatively and a group of healthy controls. On the other hand, Davies et al. (4) compared pre- and postoperative gastric emptying of solids in patients undergoing VTP-HM, and observed significantly slower gastric emptying postoperatively even after exclusion from analysis of measurements made during the first two months following the operation. The interval between VTP-HM and the gastric emptying examination in the above study quoted was as long as 104 weeks. Therefore, by setting a more definite time interval between the surgery and postoperative gastric emptying measurements, we attempted to detect what would be the direct effect of VTP-HM on gastric emptying of solids. This approach revealed the complexity of the problems involved in the examination of postoperative gastric evacuation. When all patients examined were considered as a one group, no significant change in gastric emptying was observed after VTP-HM and the average postoperative gastric emptying was also indistinguishable from that observed in normal controls. However, examination of individual post-VTP-HM gastric emptying data revealed that in as many as 10 out of 14 patients (71%) gastric evacuation was clearly abnormal (i.e. outside the two-tailed 95% confidence limit for normal values). Interestingly, either a very rapid (in four patients) or an extremely slow (in six patients) gastric emptying was found postoperatively. This observation implies that the postoperative gastric emptying of solids is very difficult to predict after VTP-HM, which should be considered a disadvantage of this surgical procedure. It would appear that adaptative processes developing within the gut should restore this VTP-HM-disturbed gastric emptying to normal, but studies by MacGregor et al. (23) and Mayer et al. (24), who observed markedly impaired gastric emptying of solids even several years after vagotomy and pyloroplasty, cast doubt on whether full normalization of gastric emptying after the VTP-HM is possible in every patient. In this context, a comparison between VTP-Cas and VTP-HM with regard to their effect on gastric evacuatory and secretory function appears to be more interesting. It should be emphasized here that the two groups of patients were comparable with respect to peptic ulcer localization; the ratio of duodenal to pyloric to gastric ulcers was 10:3:1 in the VTP-Cas group (22) and 8:4:2 in the VTP-HM group. VTP-Cas, but not VTP-HM, caused significantly slower gastric emptying than in healthy controls (22). Abnormally rapid gastric evacuation was found in only one out of 14 patients after VTP-Cas, but was seen in four out of 14 VTP-HM patients. Markedly delayed gastric emptying was found, however, in a similar number of patients: five out of 14 after VTP-Cas (22), and six out of 14 after VTP-HM. The change in the gastric emptying pattern evoked by the two surgical procedures was different. VTP-Cas resulted in a significant decrease in the shape parameter S, which was indicative of a delayed late gastric emptying phase (22), whereas after VTP-HM the S parameter tended to increase. So far we have not been able to suggest a convincing pathophysiological mechanism which could account for the differences outlined.

As can be expected on the basis of previous reports by other investigators (29, 32), the basal and penta-gastrin-stimulated gastric acid output decreased, whereas the fasting serum gastrin level and postprandial gastrin release tended to increase following VTP-HM. VTP-Cas, on the other hand, did not evoke any change in the fasting serum gastrin concentration, and elicited only a minor increase in the meal-induced gastrin output. At the same time, VTP-Cas proved to be significantly more effective in reducing the basal gastric acid output than VTP-HM. Because such factors as postoperative gastric emptying, residual gastric acid output and gastrinemia have been reported to affect the ulcer recurrence rate after surgery for peptic ulcer disease (8, 25, 27, 28); the results of this comparative study on the effects of vagotomy with two pyloroplasty variants on
gastric evacuatory and secretory functions appear to provide clinically relevant information. Thus, with regard to the magnitude of postoperative gastric acid output and gastrinemia, preference should be given to VTP-Cas over the VTP-HM procedure. With VTP-Cas reduced risk of abnormally rapid gastric emptying of solids postoperatively can also be expected. It should be pointed out, however, that the findings outlined pertain only to the results derived from examinations during the early postoperative period, and a follow-up study will have to be undertaken to confirm any possible advantages of the VTP-Cas over the VTP-HM procedure.

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