DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

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VAGOTOMY IN DUODENAL ULCER DISEASE

A STUDY OF GASTRIC ACIDITY, SERUM PEPSINOGEN I, GASTRIC MUCOSAL HISTOLOGY AND HELICOBACTER PYLORI

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List of original publications that the present thesis is based on

I. Changes of serum pepsinogen I level in patients with peptic ulcer after different gastric operations.
A. Peetsalu, A. Tamm, M. Härkönen, K. Varis, S.-L. Karonen, T. Väli, K. Villako. *Acta et comment Univers Tartuensis* 1989, 854, 38–49

II. The Effect of Vagotomy and Antrectomy on Serum Pepsinogen I and II.
A. Peetsalu, A. Tamm, M. Härkönen, K. Varis, P. Sipponen, S.-L. Karonen, T. Väli, K. Villako. *Scand J Gastroenterol* 1990, 25, 455–461

III. Long-term Effect of Vagotomy on Gastric Mucosa and Helicobacter pylori in Duodenal Ulcer Patients.
A. Peetsalu, H.-I. Maaroos, P. Sipponen, M. Peetsalu. *Scand J Gastroenterol* 1991, 26 (Suppl. 186) 77–83

IV. Postoperative Endoscopic Congo Red Test for Estimating the Completeness of Vagotomy.
A. Peetsalu, M. Peetsalu, T. Vardja. *"Eesti Arst"* (The Estonian Physician) 1992, 1, 12–15 (in Estonian, summary in English)

V. Effect of Vagotomy on Serum Pepsinogen I during the Operation.
A. Peetsalu, M. Härkönen *"Eesti Arst"* (The Estonian Physician) 1992, 2, 87-90(in Estonian, summary in English)

VI. Risk Evaluation of Postvagatomy Ulcer Recurrence by Using Endoscopic Congo Red Test and Gastric Secretion Tests.
A. Peetsalu, M. Härkönen, M. Peetsalu, T. Vardja, K. Villako and K. Varis. *Scand J Gastroenterol* 1992 (submitted for publication)

These papers are cited in the text by the Roman numerals I to VI.

Abbreviations

AE	– antrectomy
BAO	– basal acid output
DU	– duodenal ulcer
ECRT	– endoscopic Congo Red test
HP	– Helicobacter pylori
JAB	– gastroduodenostomy Jaboulay
MAO	– maximal acid output
NAO	– nocturnal 12-hour acid output
PAO	– peak acid output
P	– pyloroplasty
PV	– proximal vagotomy (= highly selective vagotomy)
S-PG I	– serum pepsinogen I
TV	– truncal vagotomy

Vagotoomia duodenaalhaavandi korral. Maohappesuse, seerumpepsinogeen I, maolimaskesta histoloogilise seisundi ja Helicobacter pylori uurimine.

Uurimise eesmärk

1. Selgitada vagotoomia mõju mao soolhappe sekretsioonile ja seerumpepsinogeen I tasemele esimese aasta jooksul pärast operatsiooni, sealhulgas vagotoomia vahetut mõju pepsinogeen I sisaldusele seerumis operatsiooni ajal.
2. Võrrelda endoskoopilise kongo punase testi, multikriteriaalse insuliintesti ja öise 12-tunnise mao soolhappe sekretsiooni reduktsioonitesti tähtsust vagotoomia täielikkuse hindamisel. Endoskoopilise kongo punase testiga ja kaugtulemuste uurimise kaudu pärast proksimaalset ja trunkaalset vagotoomiat kindlaks teha: vagotoomia inkompleetsus, inkompleetse vagotoomia alade lokalisatsioon ja suurus maokorpuse limaskestal ja selle seos retsidiivhaavandiga.
3. Uurida maohappe sekretsiooni ja seerumpepsonogeen I taset 5–12 aastat pärast operatsiooni sõltuvalt vagotoomia kompleetsusest endoskoopilise kongo punase testi alusel.
4. Teha kaugtulemuste uurimise kaudu kindlaks vagotoomia mõju maolimaskesta morfoloogilisele seisundile ja Helicobacter pylori esinemissagedusele ning intensiivsusele sõltuvalt kasutatud vagotoomia tüübist ja kompleetsusest.
5. Selgitada endoskoopilise kongo punase testi, maohappe sekretsiooni, seerum pepsinogeen I ja Helicobacter pylori kolonisatsiooni seost retsidiivhaavandi tekkimisega ja prognoosimisega.

Materjal ja metoodika

Uuriti 549 kroonilist duodenaalhaavandihaiget, neist 362 opereeritud ja 187 opereerimata.

Suurima rühma moodustasid 1976–1984 Tartu Kliinilise Haigla II kirurgiaosakonnas vagotomeeritud 341 duodenaalhaavandihaiget: 249-le tehti proksimaalne vagotoomia, neist 127 juhul koos püloroplastikaga ja 20 juhul gastroduodenos-

toomiaga Jaboulay järgi; 92 juhul tehti trunkaalne vagotoomia koos püloroplastikaga (82) või gastroduodenostoomiaga Jaboulay järgi (10). Nendel patsientidel uuriti erinevaid mao funktsionaalseid ja morfoloogilisi näitajaid enne operatsiooni ning 3 kuud, 1 aasta ja 5–12 aastat (keskmine 8 aastat) pärast operatsiooni. 21 duodenaalhaavandihaiget opereeriti 1989.–1990. aastal. Nendel uuriti vagotoomia mõju seerumpepsinogeen I-le operatsiooni ajal. 187 opereerimata duodenaalhaavandi haiget moodustasid kontrollrühma, mille najal uuriti maolimaskesta morfoloogilist seisundit ja Helicobacter pylori kolonisatsiooni 5–12 aastat pärast vagotoomiat.

Morfoloogiliste uuringute aluseks oli söögitoru, mao ja duodeenumi endoskoopiline uurimine koos proovitükkide võtmisega mao antrumi ja korpuse limaskestast. Peale maolimaskesta morfoloogilise seisundi määrati ka Helicobacter pylori kolonisatsioon ja selle intensiivsus nii mao antrumis kui ka korpuses. Kaugtulemuste uurimisel oli tähtsal kohal vagotoomia täielikkuse hindamine 270 haigel endoskoopilise kongo punase testiga. Peale selle uuriti maohappe sekretsiooni kvantitatiivselt: basaalne, maksimaalselt stimuleeritud ja öine 12-tunni maohappe sekretsioon ning seerumpepsinogeen I enne operatsiooni ning 3 kuud, 1 aasta ja 5–12 aastat (keskmine 8 aastat) pärast operatsiooni. Oluline oli selgitada nende uuringute alusel erinevate vagotoomiatüüpide (proksimaalne või trunkaalne) ja vagotoomia kompleetsuse mõju nii mao morfoloogilisele seisundile kui ka funktsionaalsetele näitajatele ning nende kasutamise võimalusi operatsioonijärgse retsidiivhaavandi prognoosimiseks.

Tulemused

1. Vagotoomia kompleetsuse määramisel on endoskoopiline kongo punase test multikriteriaalsest insuliintestist ja öisest 12-tunnisest maohappe sekretsiooni reduktsiooni testist kliiniliseks kasutamiseks sobivam ja täpsem.
2. 5–12 aastat pärast operatsiooni esineb endoskoopilise kongo punase testi tulemuste põhjal pärast proksimaalset vagotoomiat inkompleetsust sagedamini (56%) kui trunkaalse vagotoomia järel (34%).
3. Vagotoomia ei põhjusta üldiselt seerumpepsinogeen I taseme

alanemist ei lokaalselt, maokorpusest väljuvas ega perifeerse veeni veres operatsiooni ajal. Pärast operatsiooni, sõltumata vagotoomia tüübist, väheneb pidevalt seerumpepsinogeen I keskmine tase. Kuigi enamusel patsientidest seerumpepsinogeen I tase alaneb, siiski osal juhtudest seda ei esine.

4. Seerumpepsinogeen I tase 5–12 aastat pärast operatsiooni ei sõltu vagotoomia täielikkusest, mistõttu selle taseme määramine ei saa olla vagotoomia kompleetsuse näitaja.
5. Vagotoomia efekt maolimaskestale ja Helicobacter pylori kolonisatsioonile sõltub vagotoomia täielikkusest mitte aga kasutatud vagotoomia tüübist (proksimaalne või trunkaalne). Vagotoomia põhjustab: maokorpuse limaskesta atroofiat, sagedamini täieliku vagotoomia korral; Helicobacter pylori esinemissageduse vähenemist antrumis täieliku vagotoomia korral ja tõusu maokorpuses; Helicobacter pylori kolonisatsiooni intensiivsuse suurenemist nii antrumis kui ka korpuses, eriti mittetäieliku vagotoomia korral.
6. Endoskoopilise kongo punase testi põhjal on retsidiivhaavand 5–12 aastat pärast operatsiooni seotud inkompleetse vagotoomiaga. Sagedamini tekib haavand siis kui maokorpuse limaskestal on säilunud vaguse innervatsioon 20% või suuremal alal.

   Retsidiivhaavandi esinemise puhul on basaalne ja öine 12-tunnine maohappe sekretsioon ning seerumpepsinogeen I tase kõrgem. Enamasti on kõrge ka Helicobacter pylori kolonisatsiooni aste nii antrumis kui ka korpuses.
7. Retsidiivhaavandi riski selgitamiseks pärast vagotoomiat tuleks esimesena kasutada endoskoopilist kongo punase testi. Negatiivse testi korral on retsidiivhaavandi teke vähe tõenäoline. Positiivse testi korral on vaja riski prognoosimiseks määrata seerum-pepsinogeen I tase või basaalne maohappe sekretsioon kombineerituna öise maohappe sekretsiooniga.

Introduction

During the last 20 years in the surgical treatment of DU patients gastric preserving methods like vagotomy without or with drainage are widely used. The most important effects of vagotomy are the reduction of acid and pepsin outputs that bring about a long-term therapeutic effect in most DU patients. After vagotomy, a later problem is the development of recurrent ulcers whose percentage continuously increases with the time passing from the operation (Jensen et al., 1983; Adami et al., 1984; Muller and Martinoli 1985; Macintyre et al., 1990).

According to literature, there are recurrent ulcers in averagely 10% of the cases 5 years and already in 20% of the cases 10 years after PV (Hildebrandt et al., 1988). At that, a prospective randomized controlled trial study 11–15 years after the operation in DU patients showed no significant difference of recurrent ulcer rate between 3 types of vagotomy: truncal, selective or proximal (Hoffman et al., 1989). Our study results 5–12 years after vagotomy also confirm that the essential disadvantage of it is the development of recurrent ulcers (Peetsalu et al., 1990; Vardja et al., 1990).

Postvagotomy gastric secretion studies have shown that patients with recurrent ulcer tend to have higher levels of acid output (Blackett and Johnston 1981; Macintyre et al., 1990) and S–PG I (Samloff et al., 1976), and therefore it is generally believed that incomplete vagotomy is the major factor responsible for ulcer recurrences after vagotomy (Lunde et al., 1983; Holle et al., 1988) or faulty indication for the operation (Reisig et al., 1985).

Gastric acid secretion in connection with vagotomy in DU patients has been studied during many years both pre- and postoperatively, using different tests BAO, MAO, NAO, etc. The results have been contradictory concerning the prognosis of recurrent ulcers (Baron, 1978). In relation to ulcer recurrences no typical or prognostically important features have been found in the acid secretion tests, including the widely used Hollander test for estimating the completeness of vagotomy (Kjaergaard et al.,1980; Paimela et al., 1983).

The Hollander test (Hollander, 1946) has later been complemented. In addition to the stimulation of the gastric secretion

with insulin, several criteria of gastric acidity changes are taken into account as well resulting in the so-called multiple criterial insulin test. But even the complemented test is not much more reliable than the Hollander criterion alone (Hood et al., 1976). Postoperatively more sensitive and relevant to the clinical behaviour for estimating the completeness of vagotomy has been found ECRT (Saik, 1976). Information according to ECRT is semiquantitative or even quantitative. It allows one to determine the localization and size of the areas with residual vagus innervation. Also, ECRT and postoperative Hollander testing have been shown to correlate well (Saik, 1983). On the other hand, however, the agreement between ECRT, the Hollander test, and the post-vagotomy multiple criterial insulin test is not absolute in cases of incomplete vagotomy (Gallinger et al., 1979). At that, there are no data available about the use of ECRT 5 years and longer after the operation that would give an estimation of the reliability of the test in recurrent ulcer cases and in patients without recurrences. That is why ECRT was used in the present study. We also compared it to other, more widely used quantitative indicators of gastric acidity. In this study ECRT was the basis for estimating other functional and morphologic changes in the gastric mucosa after vagotomy.

Besides acid, the secretion of pepsin is also essential in the pathogenesis of ulcer. Earlier studies report that gastric pepsin levels can be estimated on the basis of S–PG I; the two are in correlation with each other (Waldum et al., 1978; Plebani et al., 1983). At the same time, S–PG I in connection with vagotomy in DU patients has a much shorter history of research than gastric acidity. It is known that the levels of S–PG I in non-operated DU patients are averagely higher than in healthy persons (Samloff and Taggart, 1987). Some studies report that S–PG I high levels correlate with ulcer recurrence (Samloff et al., 1976; Stabile et al., 1978). The literature data show that gastric acidity falls immediately after vagotomy, already at the time of the operation. Tests for checking the completeness of vagotomy during the operation are based on that phenomenon (Grassi and Orecchia, 1974). There are no data about S–PG I changes during the operation immediately after vagotomy, and for that reason it was examined in the present study. Still, the levels of S–PG I decrease after the operation that demonstrates the dependance of S–PG I on the vagal innervation (Haukland

et al., 1982; Paimela et al., 1984; Feldman et al., 1988).

However, studies have shown that postoperative S–PG I evaluation can't serve as a test for the completeness of vagotomy after PV and so replace acid secretion tests (Paimela et al., 1984; Äärimaa et al., 1987). The reason for that is evidently the absence of correlation between S–PG I and gastric acidity indicators in DU patients, both before and averagely 4 years after PV (Feldman et al., 1988). At that, there are no data about the influence of TV as compared to that of PV on S–PG I levels at the time of the operation and after it. Neither are there any data about the role of S–PG I or its connection with the development of recurrent ulcer and in prognosticating a recurrent ulcer more than 5 years after vagotomy, depending on the completeness of vagotomy in DU patients.

Gastric acid and S–PG I levels correlate well with the morphological state of the corpus mucosa: there is a continuous and significant decrease of the mean values with the development of an increasing degree of corpus atrophy (Vuoristo et al., 1991). At it, in DU patients the corpus mucosa is mostly normal or shows superficial gastritis and it remains stable until old age (Kekki et al., 1984). The effect of vagotomy on the morphological state of the gastric corpus has been studied only during a relatively short period after vagotomy and with contradictory results. Some authors have observed the development and progression of postvagotomy corpus gastritis (Äärimaa et al., 1984; Aase et al., 1985), while others found no essential differences between the operated and nonoperated patients (Dewar et al., 1983, Lygidakis 1986). There are no long-term studies about the effects of vagotomy on the gastric corpus mucosa depending on the completeness of vagotomy and also on the type of vagotomy used. But nearly all non-operated DU patients have antral gastritis (Cheli and Gjaeosa, 1986; Sipponen et al., 1989).

Since 1983, after the description and characterization of Helicobacter pylori (HP) (Warren and Marshall, 1983), a high association between the presence of HP, chronic antral gastritis and peptic ulcer is recognized (Goodwin et al., 1986; Blaser, 1987). The eradication of HP by medical treatment reduced the duodenal ulcer recurrency rate (Hamilton et al., 1986; Coghlan et al., 1987; Marshall et al., 1988) that demonstrates the role of HP in the pathogenesis of DU.

In a limited material and short follow-up period until now, it has been shown that PV does not influence the incidence rates of HP in the gastric mucosa (O'Connor et al., 1986; Petkaneshkow et al., 1990). There are no data about the effect of TV on HP colonization after the operation. The studies about the relationship between DU and HP colonization after vagotomy have been limited to the antral mucosa and fix only the positive or negative occurrence. No data are available on HP colonization in the gastric corpus mucosa after vagotomy.

Earlier research in non-operated DU (Stolte et al., 1989) and GU (Maaroos et al., 1991) patients has shown that in addition to the mere presence of HP in the stomach, the degree of its colonization intensity is essential as well. A heavy HP colonization is associated with an increased ulcer risk and aggravates the course of peptic ulcer, if present. There is no information about quantitative changes of HP after vagotomy in DU patients and its prevalence depending on the completeness and type of vagotomy, nor on its connection with ulcer recurrence.

It is clear from what has been said that a number of problems related to the effect and success of vagotomy still need further clarification. That is why the aim of the present study was to find out the effect of vagotomy on gastric acid secretion, S–PG I, gastric mucosa, and HP colonization and its intensity in different parts of the stomach during a longer period after the operation. This is the first research based on ECRT when studying long-term results of gastric functional and morphological changes depending on the completeness of vagotomy. Also the study is an attempt to characterize recurrent ulcers and to predict their development, making use of the above indicators that would lead to finding of new ways for their prevention.

The purposes of the present study are:

1. to determine the effect of vagotomy on gastric acid secretion and S–PG I during 1-st year after the operation, including its immediate effect on S–PG I level during the operation;
2. to compare ECRT, the multicriterial insulin test and the NAO reduction test as methods for estimating the completeness of vagotomy; to estimate in DU patients in a long-term period after proximal and truncal vagotomy the incompleteness of vagotomy and its location and size in the corpus

mucosa in relation to recurrent ulcer according to ECRT;

3. to determine gastric acid secretion and S–PG I levels 5–12 years after vagotomy, depending on the completeness of the latter;
4. to study the long-term effect of vagotomy on the gastric mucosal histology and HP colonization in DU patients, depending on the type and completeness of vagotomy;
5. to clarify the meaning of ECRT, gastric acid secretion, S–PG I and HP colonization for the characterization and prognosis of recurrent ulcer after vagotomy in DU patients.

Material

Altogether 549 subjects, 362 operated and 187 nonoperated DU patients were studied (Table 1). All 362 patients were operated on in the Department of Surgery of Tartu University Hospital.

The largest group was 341 consecutive vagotomized DU, including prepyloric, pyloric, bulbar and postbulbar region, patients operated on in 1976–1984 (Table 2): 249 patients had undergone PV and in addition to PV, drainage procedures had been performed in 147 of the cases (127 pyloroplasty, 20 gastroduodenostomy Jaboulay); 92 patients had undergone truncal vagotomy with drainage (82 pyloroplasty, 10 gastroduodenostomy Jaboulay). The methods of the vagotomies were strictly standardized and the operations were performed by experienced surgeons.

The patients belonging to these groups were studied in respect to different functional and morphological indicators of the gastric mucosa before the operation, and 3 months, 1 year and in a long term period of 5–12 years (mean 8 years) after the operation (publ. I, II, III, IV, VI). 21 patients were operated on in 1989–1990 (publ. V): in 15 cases the operation was PV (12 of them with drainage) and 6 cases were TV (one case with drainage and 5 with antrectomy). The influence of vagotomy on serum PG I during the operation was studied in the patients of this group. The group of non-operated patients consisted of 187 consecutive symptomatic, medically treated DU patients collected by H.-I. Maaroos. They were endoscopically examined at the Gastroenterological Department of Tartu University Hospital. Ulcer history ranged from 1–20 years, mean 3.5 years (Table 1). This group was the control group, for comparing the results of the histological findings and HP colonization in the gastric mucosa with those of the operated patients (publ. III).

Table 1

Distribution of sex and age in the studied subjects

Operated group period of operation	Number of subjects	Male/female	Mean age (limits)
I 1976 – 1984	341	298/43	41 19 – 72
II 1989 – 1990	21	20/1	41 21 – 58
III Non-operated group (controls)	187	127/60	43 18 – 78
Total number of studied subjects	549		

Table 2

Distribution of the types of the 362 operations

Operation	Time period of the operations	
	1976 – 1984	1989 – 1990
PV	92*	3**
PV + P	127	12
PV + JAB	20	–
TV + P	82	1
TV + JAB	10	–
TV + AE	–	5
Total	341	21

* in 38 cases PV with duodenoplasty was used
** in 2 cases PV with duodenoplasty was used

Methods

1. Diagnostic methods for duodenal ulcer and during follow-up period after vagotomy.

In the nonoperated subjects (controls) with DU the ulcer was diagnosed endoscopically. In the operated DU patients, the ulcer was diagnosed mainly endoscopically, in a few cases (18) roentgenologically, and confirmed at the operation. After vagotomy in the follow-up period (3 months, 1 year and 5–12 years after the operation) the examination of the patients, including an endoscopic examination, was performed in outpatient conditions. The presence or absence of recurrent ulcer was determined endoscopically, the morphological state of the gastric antral and corpus mucosa was evaluated by two biopsy specimens taken from both parts of the stomach; and from 1988 onwards, the completeness of vagotomy was estimated by ECRT. Olympus GIF–Q oesophago-gastroduodenoscopy was used, biopsy specimens were obtained using biopsy forceps FB–24 K.

2. Gastric acid secretion tests.

All gastric acid secretion studies by gastric probing were performed in in-patient conditions.

2.1. Basal acid output, maximal acid output and nocturnal acid output.

The gastric juice was collected from a previously emptied stomach during 60 min for BAO. MAO was determined by collecting gastric juice during two 30 min fractions after pentagastrin stimulation 6 μg/kg intramuscularly. NAO was determined by collecting gastric juice from a previously emptied stomach during 12 hours from 8 p.m. to 8 a.m. The position of the tube in the stomach was checked roentgenologically and continuous aspiration of the gastric juice was used in all cases.

2.2. Hollander test.

In the DU patients operated during 1981–83, the completeness of vagotomy 1 year after the operation was determined by the Hollander test (publ. I). The gastric juice for

the Hollander test (Hollander, 1948) was collected from a previously emptied stomach during 60 min (4x15-minute samples) for BAO. After that insulin was given 0.2 IU/kg intravenously. Its effect was confirmed by a blood glucose estimation. A concentration less than 2.5 mmol/l was the criterion of an adequate insulin effect. The gastric juice was collected during 2 hours after the insulin stimulation. The test was considered positive if there was an increase of 20 mmol/l in titrable acidity in any two consecutive 15-minute samples in the 2 hours after the intravenous injection of insulin over the mean acidity of two 15-minute basal samples. When the basal samples contained no free acid then the test was considered positive if the post-insulin acidity was more than 10 mmol/l. A positive response (= incomplete vagotomy) during the first hour after the stimulation was regarded as early positive and during the second hour as late positive (Johnston et al., 1967).

2.3. Endoscopic Congo Red test.

During the study of the long-term results from 1988 onwards, the completeness of vagotomy by ECRT was estimated according to Donahue et al., 1977 in basal conditions without drug stimulation of the gastric acid secretion (publ. III, IV and VI). After aspirating all the fluid in the stomach, solution of 0.5% Congo Red in 5% bicarbonate is sprayd through the endoscope to cover the gastric corpus mucosa. Any area of the corpus mucosa which turns black (pH<3.0) within the first 2–3 min is considered as positive (= intact vagal innervation, or incomplete vagotomy). When no changes in the red colour are seen within 2–3 min, (pH>3.0), the test is considered as negative (= denervated corpus, or complete vagotomy).

2.4. Multicriterial insulin test.

The criteria are: acid output in the first hour 5 mmol more than in the basal hour after insulin stimulation, according to Clark and Murray, 1963; acid output more than 2 mmol in the 2 hours after insulin stimulation according to Stempien et al., 1958; and acid output in any hour 2 mmol more than in the basal hour before insulin stimulation according to Bank et al., 1967. The test was considered as

positive (= incomplete vagotomy) when one from three criteria was positive at the individual level.

2.5. Nocturnal acid output reduction test.

The result was considered as positive (= incomplete vagotomy) when the reduction of NAO was less than 60 per cent compared with the preoperative NAO level (Dragsteldt et al., 1947)

3. Determination of serum pepsinogen I.

Fasting S–PG I was examined in the Department of Clinical Chemistry, Helsinki University by the radioimmunoassay methods by M. Härkonen. The normal values for S–PG I are 50–150 µg/l according to Tamm et al., 1984.

4. Estimation of serum pepsinogen I in gastric corpus venous blood and effect of vagotomy on serum pepsinogen I during the operation.

During the operation blood samples were taken from the two gastric veins and from the peripheral vein immediately after laparotomy. The second blood samples were obtained from the gastric corpus vein and from the peripheral blood immediately after vagotomy. In all patients the surgery was carried out in as standard as possible conditions of anesthesia, avoiding the use of atropine or other substances with a similar effect. The technique used for obtaining venous blood was the one described by Cox et al., 1967 and Peetsalu, 1972.

The aim was to obtain blood flowing out of 2 different regions of the stomach: from the lesser curvature and the greater curvature of the gastric corpus. In order to do that, selective puncture was performed on the gastric vein branches passing through the gastric wall (rr. gastrici). The course of these vein branches is perpendicular to the gastric wall and longitudinal to the gastric veins: v. gastrica sin in the lesser curvature and v. gastroepiploica sin in the greater curvature. The blood in them (rr. gastrici) is not mixed with the venous blood from the adjacent regions.

5. Histological state and Helicobacter pylori colonization in gastric mucosa.

The biopsy specimens were fixed overnight in neutral buffered formalin and were stained for morphological and HP examination by hematoxylin-eosin and Giemsa methods. A blind examination was made of all specimens, two from the antrum and two from the corpus. The histology was studied by P. Sipponen from Jorvi Hospital, Espoo, Finland and HP pylori colonization by H. Maaroos from the Department of Internal Medicine, University of Tartu.

The histology and HP colonization in the gastric antral and corpus mucosa were classified traditionally as described previously (Kekki et al., 1987; Sipponen et al., 1990; Maaroos et al., 1990).

Histology: Normal = no loss of glands and no round cell infiltration; superficial gastritis = accumulation of round cell (infiltration) in the lamina propria without loss of mucosal glands; atrophic gastritis = loss of glands.

HP colonization: The amount of HP was estimated semiquantitatively (Stolte et al., 1989) by microscopic counting of the number of bacteria and scoring them as follows: abscence of microbes (grade 0); small amounts (grade 1) = less than 20 microbes per field; moderate amounts (grade 2) = 20–60 microbes per field; and large amounts (grade 3): more than 60 microbes per field. The microscope with an objective with 40× and an ocular with a 10× magnification was used. Both in the antrum and corpus biopsy specimens of at least two fields were examined. It HP colonization was patchy, the grade was classified according to the most pronounced colonization.

Table 3 shows the distribution of the number of methods used and the examination times in the subject.

6. Statistical methods.

The significances were calculated by using Student's t test (publ. I, III, IV). Different nonparametric statistical methods were used for testing the significance of differences: Chi-square test (publ. II, III), Mann-Whitney U test for paired and Wilcoxon test for unpaired groups (publ. II, V, VI). The correlations between the different parameters were tested by Spearman rank or Kendall test (publ. I, II, III, V, VI). p values below 0.05 were considered as significant.

Table 3

Distribution of the numbers of each method used and the examination times in subjects

Study subjects	n	Method	Total number	Time of the examination					
				Before operation	During the operation		3 months after	1 year after	5–12 years after (median 8 years)
					Before vagotomy	After vagotomy			
Operated	362								
		Histology	347	56	–	–	–	32	317
		HP	317	–	–	–	–	–	317
		S–PG I	143	96	21	14	66	61	39
		BAO	108	103	–	–	70	67	30
		MAO	108	104	–	–	70	65	30
		NAO	35	32	–	–	–	–	27
		Hollander test	67	–	–	–	–	67	–
		Multi criterial insulin test	30	–	–	–	–	–	30
		NAO reduction test	11	–	–	–	–	–	11
		ECRT	271	–	–	–	–	–	271
Nonoperated	187								
		Histology	187						
		HP	187						
Total number of subjects	549								

Results and Discussion

Part I

Effect of vagotomy on gastric acid secretion and serum pepsinogen I during 1-st postoperative year in duodenal ulcer patients.

1. Vagotomy and gastric acid secretion

It can be seen from literature that vagotomy reduces BAO 80–90% in most cases (Creenall et al., 1977; Kuzin and Postolov, 1980). After all types of vagotomy, the acid response to stimulants of gastric secretion MAO is also markedly reduced but to a lesser extent than BAO: to an average of 60–70% (Mason et al., 1968; Cowley et al., 1973). The given data show that BAO is mainly and more controlled by vagal tone than MAO (Dragstedt et al., 1947; Varis et al., 1988).

The results of the present research agree with what has been said above (publ. II). Compared to the preoperative levels, both BAO and MAO decreased significantly ($p<0.01$) while the fall of BAO was somewhat bigger than that of MAO by the 3rd postoperative month, with the mean respective values of 91% and 77%. Since immediately after the operation during the first postoperative year no atrophic changes in the gastric corpus were observed (publ. II), the effect of vagotomy directly accounts for the fall of gastric acidity. At the same time, changes in the gastric acidity during the first 3 postoperative months did not depend on the type of vagotomy used, i.e. there was no significant difference between the results of PV and TV (publ. I). Further, from the 4th month to 1 year there is a small increase in the levels of BAO and MAO. In the case of BAO the increase is statistically significant ($p<0.01$) although it still remains significantly below the preoperative levels ($p<0.01$).

By the end of the first year 34% (23/67) of the subjects proved to have incomplete vagotomy on the basis of the Hollander test. A similar rise in gastric acid secretion and number of incomplete vagotomies according to the Hollander test at the end of the first postoperative year and even later has been described also elsewhere (Jordan and Thoznby, 1986; Staël von Holstein et al., 1987). In this study, we did not investigate the causes of the gastric acidity rise after vagotomy, although

different mechanisms for such a rise have been suggested (Jordan, 1976). The data in literature show, however, that high gastric acid values after vagotomy like high BAO and incomplete vagotomy play an important role in the development of recurrent ulcer (Blackett and Johnston, 1981; Nylamo, 1987).

Therefore, clinical gastric acid secretion tests are a means for studying the predictive value of postoperative testing for ulcer recurrencies for controlling the efficacy of the surgeon's technique, and finally, for discovering the presence of residual vagal innervation in the gastric corpus mucosa (Graffner et al., 1986), if any. It is essential, however, to choose the right test for determining the completeness of vagotomy.

2. Vagotomy and serum pepsinogen I during the operation.

Gastric acidity falls immediately after vagotomy, already at the time of the operation. Tests for checking the completeness of vagotomy during the operation are based on that phenomenon (Grassi and Orecchia, 1974). There are no direct data about how much PG I is secreted into the gastric veins by different gastric corpus regions and how it is reflected in the peripheral circulation. In the present part an analysis is presented on: first, S–PG I levels locally in the venous blood flowing out from the lesser and the greater curvature of the gastric corpus; second, how those levels correlate with simultaneous peripheral venous blood data, and third, if vagotomy has a direct effect on the amount of S–PG I secreted during the operation in DU patients.

This study shows that S–PG I mean values both in the lesser and the greater curvature of the gastric corpus venous blood are 2.5–3.1 times higher than in the peripheral venous blood: 362±42 μg/l, 460±61 μg/l and 146±11 μg/l, respectively ($p<0.05$). It seems that the concentration of S–PG I flowing out of the gastric corpus into the general circulation (peripheral blood) is determined by the dilution effect and the renal clearance (Waldum et al., 1982; Kate et al., 1986). The values of S–PG I in the gastric corpus venous blood both in the lesser and the greater curvatures as well as their total sum show a significant correlation with S–PG I in the peripheral blood; $r=0.5961$ $p<0.01$, $r=0.3284$ $p<0.05$ and $r=0.6036$ $p<0.05$, respectively. It confirms that the S–PG I values determined in the peripheral blood reflect adequately the S–PG I level in the blood flowing

out of the gastric corpus, but after the dilution effect and the renal clearance as described above. At that very good correlations ($r=9171$ $p<0.001$) between the S–PG I from the lesser curvature and the greater curvature were observed. During the operation (Fig. 1), immediately after PV the local mean S–PG I rises significantly in the blood of the vein leaving the greater curvature of the gastric corpus (a rise in 7 cases from 8) and in the peripheral blood (a rise in all 8 cases) ($p<0.05$). After TV there was no significant rise in the mean S–PG I either in the blood flowing out from the gastric corpus (a rise in 4 cases of 6) or in the peripheral blood (a rise in 5 cases from 6) ($p>0.05$). Since no analogical effect was observed after truncal vagotomy, the S–PG I rise after PV cannot be accounted for by the severance of the vagal innervation.

There must be some other reason for the S–PG I rise during the operation. Most likely it appears due to the 70 min (on the average) mechanical manipulations: the trauma to the gastric corpus during PV, damage to the mucosa including the chief cells and the mucous neck cells, and the release of S–PG I into the venous blood from them. The local rise of S–PG I is immediately reflected in the peripheral blood, although after the dilution effect. In case of truncal vagotomy the mechanical trauma to the gastric corpus is much smaller and shorter lasting (15 min, on the average), and the direct damage to the gastric mucosa is much more limited.

On the other hand, the immediate effect of vagotomy on the gastric blood supply may play a role here: due to the opening of shunts the mucosal blood supply will decrease essentially (Bell and Battersby, 1968). Therefore, the use of truncal vagotomy is effective in order to arrest bleeding from gastric mucosal lesions (Sullivan and Wadell, 1968; Drapanas et al., 1971).

The results show that in general immediately after vagotomy during the operation S–PG I does not decrease either locally, in the gastric veins, or in the peripheral venous blood. Obviously the inhibitory effect of vagotomy on the synthesis of pepsinogen in the gastric corpus manifests itself slowly, not as quickly as on gastric acidity.

3. Vagotomy and serum pepsinogen I after the operation.

The data of this study show that vagotomy has a significant diminishing effect on the mean S–PG I during one year after the

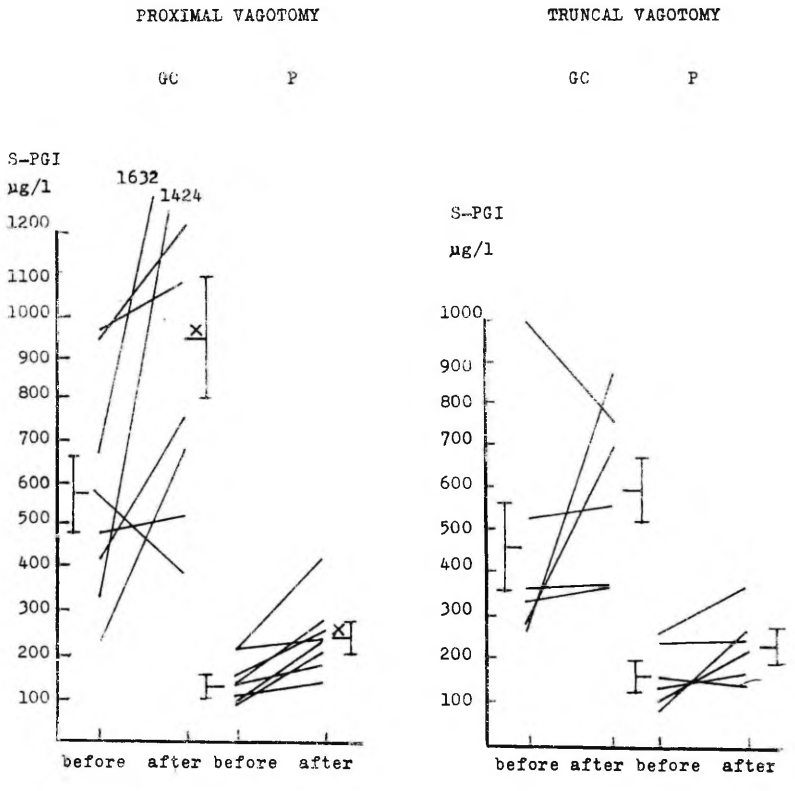

Fig. 1. S-PGI levels in gastric corpus (GC) and peripheral venous blood (P) before and immediately after proximal and truncal vagotomy during the operation: individual changes and mean±SE. $x_p<0.05$ levels after versus before vagotomy.

operation (publ. II). The decrease of the mean S–PG I was 56% compared with the preoperative levels ($p<0.001$). The average postoperative change in S–PG I does not depend on the completeness of vagotomy according to the Hollander test. ECRT as more sensitive for estimating the completeness of vagotomy was not used in the patients studied in 1981–1983. But our results indicate that the vagal tone has a significant effect on the synthesis and/or release of PG I from the peptic cells and further on the mean S–PG I level. S–PG I tends to increase during the development of superficial gastritis (Varis et al., 1989) and decrease during the progress of corpus mucosal atrophy. None of the DU patients had atrophic gastritis during the one-year period of observation, hence, the decrease in S–PG I after the operation cannot be explained by corpus mucosal atrophy.

The present study is the first that has made it possible to compare the effects of two different vagotomy types, PV and TV, on S–PG I over a 12-month follow-up period (publ. II). Proximal vagotomy excludes parasympathetic innervation from the gastric body mucosa and truncal vagotomy from all parts of the stomach and duodenum. Both operations reduce the mean S–PG I significantly while the reduction observed at the end of the first postoperative year does not depend on the type of vagotomy. The present study confirms the earlier observation that PV reduces S–PG I (Haukland et al., 1982; Paimela et al., 1984; Äärimaa et al., 1987; Feldman et al., 1988) and shows for the first time that truncal vagotomy has a similar effect.

4. Correlation between gastric acid secretion and serum pepsinogen I before and one year after vagotomy.

A poor correlation was observed between S–PG I and acid output (BAO and MAO) before and 1 year after the operation in DU patients in this material (publ. II). Similar findings have been published earlier (Goedhard et al., 1985; Feldman et al., 1988). The data show that in this consecutive series of DU patients preoperative normal DU values of S–PG I were more frequent than high ones, occurring in 54% and 46% of the cases, respectively (publ. I), as has also been reported earlier (Feldman et al., 1988). Our study confirms the view that a low S–PG I can exclude a diagnosis of duodenal ulcer (Samloff and Taggart, 1987). Unlike S–PG I, preoperative gastric acid in the same

consecutive DU patients was most frequently high, less often normal or low (in 57%, 33% and 10%, respectively). Such a variability in the levels of gastric acid and serum pepsinogen has been reported earlier by Feldman et al., 1988, who show also differences in different ethnic groups.

The mean levels of both S–PG I and gastric acid output are significantly higher in non-operated DU patients than in controls. But it is clear that in any one person a high S–PG I is not a reliable indicator of gastric acid hypersecretion, and a normal level is not a reliable indicator of normal acid secretion (Plebani et al., 1983; Feldman et al., 1988).

The present study demonstrates for the first time that the behaviour of S–PG I after vagotomy (already during the operation and later during one year) differs from that of gastric acid (Fig. 2). While the mean S–PG I keeps decreasing during 1 year, the mean levels of BAO and MAO increase from the 4th to 12th month after an initial marked fall, i.e. from the operation until the 3rd month. The data of the study show that the production of gastric acid is more inhibited by vagotomy than that of S–PG I is, and this discordance is the reason for the poor correlation between S–PG I and acidity. It is further confirmed by the fact that while 3 months after vagotomy BAO had fallen in all the subjects, the individual course of S–PG I after the operation was divergent: it did decrease in most patients but either remained the same or even increased in others (publ. I). Obviously the heterogenity of peptic cell populations, the production, storing and release of S–PG I from the chief cells and mucous neck cells, and the metabolism of pepsinogens is more complicated than the secretion of hydrochloric acid from just one separate cell population, the parietal cells. This may explain why the secretions of S–PG I and acid correlate poorly and why all attempts to replace acid secretion studies by more convenient S–PG I measurements have failed so far.

Accordingly, not only the acid secretion but also the level of S–PG I reflects the morphologic and functional state of the gastric mucosa, although indirectly. It means that both the secretion of acid and S–PG I have to be considered together in order to assess the morphologic and functional state of the gastric corpus mucosa and to predict or characterize ulcer recurrence after vagotomy.

Moreover, as shown by this study, the secretion of gastric

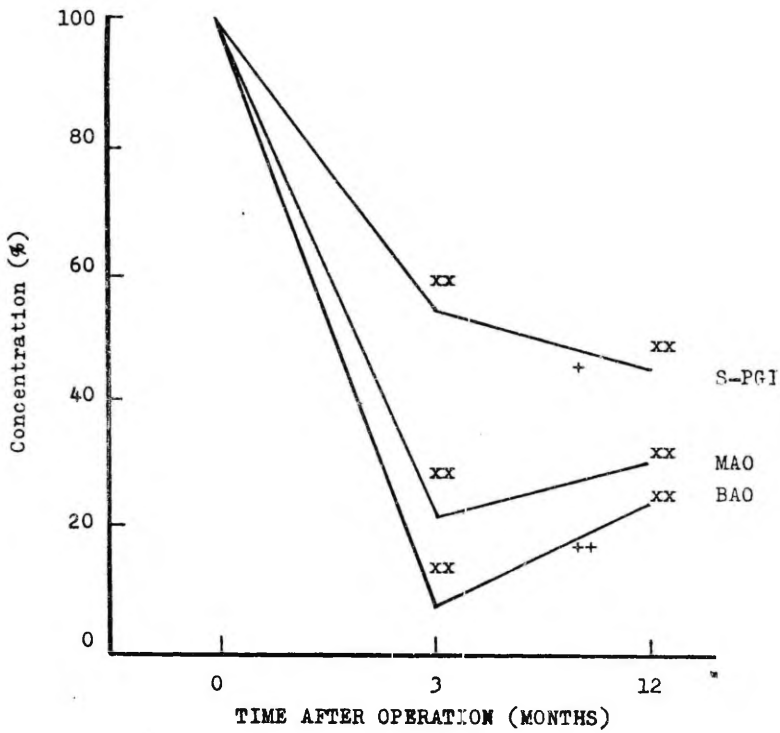

Fig. 2. Mean postoperative changes (in percentage) in S-PG I and BAO and MAO in DU patients after proximal vagotomy. Preoperative values are taken as 100%. $^{xx}p<0.01$ compared with the preoperative value; $^{+}p<0.05$ between 3- and 12-month values after the operation; and $^{++}p<0.01$.

acid is more vagally controlled than that of S–PG I. At the same time, however, after a marked initial decrease of BAO, in this material an increase in gastric acid secretion starts from the 3rd month onwards. As reported in literature, the increase continues for a longer period both after PV (Holst-Christensen et al., 1977) as well as after TV (Jordan and Condon, 1970; Smith et al., 1972). Therefore, it is important to know in connection with vagotomy how much such an acid secretion rise after the operation is dependant on vagal residual innervation, a rise that later may cause the development of recurrent ulcer.

Todate, the most widely used vagotomy completeness test has been either the Hollander test, or some of its variants. They are based on the measurements of gastric secretion after an insulin stimulation. That was also the test used in this study in 1981–83 for estimating the completeness of vagotomy after the operation. However, insulin hypoglycemia does not selectively stimulate the vagus in man and thus one cannot distinguish the vagal effect from the non-vagal one (Hodge et al., 1972; Saik, 1983). That is why in the following parts of this study the ECRT test as more sensitive and specific for estimating the completeness of vagotomy was used in studying the long-term results of the operation depending on the completeness of vagotomy.

Part II
Completeness of vagotomy according to endoscopic Congo Red test 5–12 years after vagotomy

1. Comparison: NAO reduction test, multicriterial insulin test and ECRT for estimating the completeness of vagotomy.

As can be expected, the results of estimating the completeness of vagotomy depend on the susceptibility and preciseness of the test used on the one hand, and on the patients studied, on the other. In comparing the tests for estimating the completeness of vagotomy the data from recurrent ulcer patient pool appear to be the most objective.

In our material nearly all recurrent ulcer patients (18/19) had incomplete vagotomies according to ECRT, whereas this percentage was smaller on the basis of multicriterial insulin test, and still smaller by the NAO reduction test (publ. IV). ECRT results, however, have to be considered more reliable since

quantitative vagotomy-completeness tests show not only vagus-stimulated but also non-vagally induced gastric acid secretion (Hodge et al., 1972) due to increased gastrin levels, as for example, after vagotomy (Thompson et al., 1978). Besides, in using quantitative methods, misleading results may be due to the loss of gastric juice during the examination, especially when vagotomy is performed together with pyloroplasty, or due to the duodenogastric reflux (Faber et al., 1975; Bateston and Bouchier, 1981). ECRT, however, determines the vagally stimulated gastric acid secretion. That has been confirmed by the examinations during the operations (Donahue et al., 1986). Moveover, the increased level of gastrin after vagotomy cannot lead to false positive results in ECRT as this would cause diffuse staining rather than the specific "patchy" distribution of positive-noted areas (Saik, 1983) as is demonstrated by our results as well. Besides, ECRT results are not affected by the loss of gastric juice and duodenogastric reflux.

The above-given reasons can evidently explain the difference in estimating the completeness of vagotomy between the multicriterial insulin test and the NAO reduction test, when compared to ECRT. Consequently, ECRT has to be regarded as a reliable basis for estimating the completeness of vagotomy, characterizing recurrent ulcers and predicting their development.

2. Completeness of vagotomy after proximal vagotomy and truncal vagotomy, and ulcer recurrency.

After vagotomy different routine control tests are widely used, primarily for checking up the technique of vagotomy, and for identifying the patients who might develop recurrent ulcer even if there are no complaints at first. When complaints arise after the operation, it is essential to try and find out if they are due to recurrent ulcer and which is their connection with the residual vagal innervation. Answers to these questions are most important in prognosticating the further course of the disease and in tactics for its treatment.

The sensitivity of quantitative gastric secretion tests is low for predicting the results of surgery both after TV (Kronborg, 1972) and after PV (Paimela et al., 1983). Today only endoscopic examinations can be relied on in order to discover recurrent ulcers and other mucosal changes, since the former may be

asymptomatic in part of the cases (Muller and Martinoli, 1985).

Thus, the advantage of ECRT appears to lie in getting a visual survey of the esophageal, gastric and upper duodenal mucosa with simultaneously locating the remaining vagally innervated areas that produce gastric acid pH<3.0.

The Congo Red test is based on the spontaneous secretion of gastric acid in basal conditions, thus demonstrating vagal activity (Kusakasri et al., 1972). ECRT results in patients with incomplete vagotomy are reproduceable in repeat examinations and hence demonstrate the stability of the test (Saik et al., 1982). Immediately after the operation, ECRT has shown incompleteness of vagotomy in 11% of the cases (Saik et al., 1982). In this study averagely 8 years after the operation the frequency of incomplete vagotomy had markedly increased — to 50% (135/271) of the cases (publ IV).

A nearly analogical increase in the frequency of incomplete vagotomy has been described also on the basis of the positive Hollander test both after proximal vagotomy (Lyndon et al., 1975) and after truncal vagotomy (Jordan and Condon, 1970).

The cause for such a rise in ECRT and in positive Hollander tests after vagotomy is uncertain. Mechanisms that have been proposed to explain the rise for Hollander test are: increase of gastrin (Jordan, 1976), loss of a fundic inhibitory reflex (Debas, 1983), and reinnervation of the fundus gland after the vagotomy (Joffe et al., 1982; Valentin et al., 1987).

According to expectations incomplete vagotomy was considerably more frequent after proximal than after truncal vagotomy, in 56% and 34% of the cases, respectively. That difference has not been described earlier on the basis of ECRT (P. Saik, 1982). One possible cause for the difference may be the more complicated technical side in performing PV when compared to TV. At that it has been shown that the most important single factor in determining the rate of incomplete vagotomy is the individual surgeon himself (Johnson and Goligher, 1971). It has been shown earlier that pyloroplasty may affect the completeness of vagotomy as well (Yoshida et al., 1988). In our material the use of pyloroplasty in addition to proximal vagotomy does not affect the completeness of vagotomy: incomplete vagotomy by ECRT was found in 54% (26/48) after PV and also in 54% (54/100) of cases after PV together with pyloroplasty.

From the point of predicting recurrent ulcers it is important

that ECRT makes it possible to ascertain the location and the size of the incomplete vagotomy area(s) in each individual patient. The areas of incomplete vagotomy were predominantly (after PV in 82% of cases and after TV even more) seen in the upper part (mainly on the back wall) of the gastric corpus, and in one-third of the cases in the lower part of it (Table 4). This result could be expected. Since performing vagotomy in the distal part of the esophagus and in the cardiac and fundus regions is technically the most difficult stage of the operation (Johnston, 1986), it explains why incomplete vagotomy areas are most frequently observed in the upper back wall of the gastric corpus. The difficulty is due to the great variability of the vagus fibres passing from the distal esophagus into the gastric corpus (Johnson, 1980; Muller and Martinoli, 1985; Sibul, 1985). On the other hand, however, vagus fibers may occur also intramurally between the esophageal muscle fibres (Loup et al., 1977; Loeweneck, 1980). Therefore the importance of performing skeletonization of the distal 5–7.5 cm of the esophagus is stressed, in order to obtain a complete vagotomy (Goligher, 1974; Hallenbeck et al., 1976). The other suggested variant — circular myotomy in the distal esophagus to ensure the completeness of vagotomy in this region (Schreiber and Schumpelick, 1986) — is not widely practiced due to possible complications. What has been said above, however, does not exclude that during 5–12 years after the initial complete vagotomy vagal reinnervation of the fundus gland has taken place, as described in the literature (Joffe et al., 1982; Valentin et al., 1987). The problem needs futher clarification. Since performing vagotomy in other gastric corpus regions is technically simpler, incomplete vagotomy areas are observed there considerably less frequently.

Nearly all (18/19) recurrent ulcers are connected with the remaining vagal innervation in the gastric corpus. In the one recurrent ulcer case in a stomach where the vagotomy proved to be complete, the recurrence was caused by chronic use of ulcerogenic medicaments on the background of low gastric acid values. The toxic effect of ulcerogenic medicaments on the gastric mucosa has been described earlier, too (Feifel and Koller, 1982), even in the case of achlorhydria in the stomach (John and McDermott, 1970).

However, out of all cases of incomplete vagotomy by ECRT

Table 4

Location and size of ECRT–positive (incomplete vagotomy) areas in the gastric corpus mucosa

ECRT–positive areas in gastric corpus mucosa		Proximal vagotomy			Truncal vagotomy		
Location	Size	n	(%)	Recurrent ulcers	n	(%)	Recurrent ulcers
Upper part	large*	22	(20%)	8	7	(28%)	3
	small**	52	(47%)	3	10	(40%)	1
Lower part	large	–		–	–		–
	small	20	(18%)	2	2	(8%)	–
Upper and lower part	large	2	(2%)	–	3	(12%)	1
	small	14	(13%)	–	3	(12%)	–
Total		110	(100%)	13	25	(100%)	5

* More than 20% of the corpus area (by subjective estimation)

** One or several areas ∅ 1 – 30 mm

recurrent ulcer patients only account for 13% (18/135). Nearly similar results have been reported before on the basis of the Hollander test (Cowley et al., 1973). It means that in the large majority of incomplete vagotomy cases the vagotomy has been sufficient to prevent the recurrence of ulcer during a long-term period after the operation. The development of recurrent ulcer in the presence of areas with residual vagal innervation depends not so much on the type of the vagotomy as on the size of such areas in the gastric corpus mucosa. Recurrent ulcers are more frequent in large areas of incomplete vagotomy involving 20% or more of mainly the upper part of the gastric corpus mucosa in 33% of the patients after proximal vagotomy and in 40% after truncal vagotomy, as it has been described also elsewhere (Saik, 1983). In case of small incomplete vagotomy areas the rate of recurrent ulcers in significantly lower, in 6–7% of the cases.

It is of some interest that in our material recurrent ulcers developed after proximal vagotomy in two patients with a relatively small area of vagal innervation in the lower part of the gastric corpus on the side of the greater curvature. Such cases have been explained by the vagal secretory innervation passing along the right gastric-epiploica vessels into the gastric corpus (Rosati et al., 1976). That is why it has been advised that those vagal fibers should be severed as well, besides the ordinary vagotomy, that is, a so-called extended proximal vagotomy should be performed (Rosati et al., 1976, Donahue et al., 1987). Still, the necessity for such operations has not been confirmed by prospective gastric secretion studies that find no difference between an ordinary PV and an extended PV (Braghetto et al., 1988). At that it is necessary to stress that an extended PV is an easy and fast procedure that can usually be performed without any complications (Braghetto et al., 1988) and that can reduce the number of incomplete vagotomy cases.

However, data suggest that small areas of incomplete vagotomy can hardly be the only cause for recurrent ulcers. It is possible that a certain role is played here by the protective mechanisms of the mucosa and by other reasons that have not been dealt with in the current paper. A further follow-up and additional studies will probably cast light on the part of small incomplete vagotomy areas in the results of surgery in these patients.

Part III

Completeness of vagotomy and its effect on gastric acid secretion, serum pepsinogen I, gastric mucosal histology and Helicobacter pylori colonization 5–12 years after operation

1. Long-term effect of vagotomy on gastric acid secretion.

Our results show (Table 5) that in the incomplete vagotomy cases (with or without recurrent ulcer) and in the complete vagotomy cases the means of all three parameters of gastric acid secretion BAO, MAO and NAO are significantly lower in a long-term period after vagotomy than the preoperative levels were. In this material recurrent ulcers were connected with incompleteness of vagotomy and the smallest postoperative reduction of mean gastric acid secretion BAO, MAO and NAO when compared to the incomplete and complete vagotomy cases without recurrence, 52–56%, 69–87% and 70–90%, respectively (Table 5). It turned out that the patients with recurrent ulcer showed higher postoperative mean acid secretion levels in case of all three parameters (BAO, MAO and NAO) as compared to the patients without recurrence. As could be expected in our material ECRT reflects also the quantitative changes of the mainly vagally controlled BAO and NAO 5–12 years after vagotomy at the mean level. Significant differences are found in NAO values, where in recurrent ulcer patients the mean of the postoperative NAO were significantly higher than those in the complete vagotomy cases, 22.8±4.5 mmol/12 h and 3.7±2.0 mmol/12 h, respectively ($p<0.05$). These differences in BAO values were smaller. There were no significant differences in MAO values between incomplete vagotomy (with or without ulcer recurrence) and complete vagotomy patients. A certain reason for the considerable difference between complete and incomplete vagotomy values may lie also in the different morphological state of the gastric corpus mucosa. In our material 5–12 years after complete vagotomy, atrophy (up to severe degrees) of the gastric corpus mucosa is significantly more frequent than after incomplete vagotomy, in 29% and 12% of the cases, respectively (publ. III).

Since in complete vagotomy cases the vagally stimulated production of acid is excluded, there must obviously exist other reasons that account for the gastric acid secretion levels in those

Table 5

Pre- and postoperative BAO, MAO, NAO and S–PG I (mean±SE) in incomplete vagotomy patients with recurrent ulcer (Group A) or without recurrent ulcer (Group B_1), and in complete vagotomy patients without recurrent ulcer (Group B_2)

Test	Preoperative data			Postoperative data		
	Groups			Groups		
	A	B_1	B_2	A	B_1	B_2
BAO (mmol/h)	5.4±1,0	6.8±1.4	5.5±0.9	2.4±0.6[1]	0.9±0.4[2]	1.2±0.4[2]
MAO (mmol/h)	22.0±2.8	22.5±2.9	19.5±3.2	10.6±1.8[1]	7.0±1.7[2]	5.8±3.3[2]
NAO (mmol/12h)	50.6±7.6	44.3±13.2	36.6±8.0	22.8±4.5[1]	13.8±2.7[1]	3.7±2.0[2,3,4]
S-PGI (µg/l)				146.5±16.2	91.0±7.7[5]	118.4±12.3

[1] $p<0.05$ preoperative vs postoperative level
[2] $p<0.01$
[3] $p<0.05$ postoperative A vs B_2
[4] $p<0.05$ postoperative B_1 vs B_2
[5] $p<0.01$ postoperative A versus B_1

subjects. One of the possible causes might be the rise in gastrin both after PV as well as TV (Lyndon et al., 1974; Thompson et al., 1978). Such an increase in the acid secretion in complete vagotomy cases is, however, too low for causing the development of recurrent ulcer. In cases of incomplete vagotomy, though, both vagally and non-vagally stimulated gastric acid secretions combine. Reaching a definite level it can cause or contribute to the development of recurrent ulcer in a certain part of the patients, may be combined with other factors. Our results show that recurrent ulcer develops in incomplete vagotomy cases after PV in 10% of the cases and after TV in 20% of the cases. It means that besides ECRT in incomplete cases, in such patients it is necessary to determine also the gastric acid secretion and to decide which values are predictive for the development of recurrent ulcer.

Several studies present the prerequisite gastric acid reduction for different parameters both for estimating the completeness of vagotomy as well as for prognosticating recurrent ulcers (Feifel and Koller, 1982; Raab and Stützer, 1986; Vinz et al., 1988). In the absence of preoperative hydrochloric acid data as for example in case of emergency operations, such calculations of gastric acid reductions can't be made. Therefore it is essential to have, in each individual case, a gastric acid test or a combination of tests that would make it possible to judge on the causes for or prognosticate the development of recurrent ulcer. The present study shows that gastric acidity BAO>1.5 mmol/h together with NAO>30 mmol/12 h has the best discriminatory ability for the prognosis of ulcer recurrences, with a sensitivity of 80% and specificity of 81%. Both the sensitivity and specificity of the other tests are lower (publ. VI).

2. Long-term effect of vagotomy on serum pepsinogen I.

According to literature (Feldman et al., 1988), in vagotomized patients after the initial decrease the mean S–PG I rises somewhat while still remaining considerably lower 4 years after the operation than before it. The causes for such a rise in S–PG I are uncertain. The above given study did not take into account the completeness of vagotomy. In the present study (publ. VI), 5–12 years after vagotomy high S–PG I values were somewhat more frequent in incomplete (7/26) than in complete vagotomy cases (2/13) by ECRT. This difference, between the

means of S–PG I of the two groups, however, was not statistically significant, 118±10 μg/l, 118±12 μg/l, respectively ($p>0.05$). That proves what has been said earlier, namely, that the levels of S–PG I after the operation cannot be used as an indicator of the completeness of vagotomy (Äärimaa et al., 1987). On the other hand, complete vagotomy does not guarantee the appearance of lower S–PG I values in DU patients during a longer period after vagotomy. Evidently there are also some other mechanisms involved in the regulation of S–PG I that are not governed by vagal innervation.

At that, in this study, 5–12 years after vagotomy the mean S–PG I in patients with recurrent ulcer was significantly higher than in patients without recurrent ulcer: 146±16 μg/l and 104±10 μg/l ($p<0.05$). It follows from here that generally in the development of recurrent ulcer, higher S–PG I levels are more definitive than lower ones. Although 5–12 years after vagotomy in recurrent ulcer cases S–PG I values above normal (54%, 7/13) were more frequent than in cases without recurrence (8%, 2/26), still the levels of S–PG I alone are not decisive in the development of recurrences. This is confirmed by the fact that two patients with high S–PG I levels did not have recurrent ulcers 5–12 years after vagotomy (publ. VI).

3. Long-term effect of vagotomy on gastric mucosal histology.

In this part the long-term effect of vagotomy on the morphology of the antral and corpus mucosa is analyzed with a special emphasis on the completeness of vagotomy and the type of vagotomy used in DU patients.

Chronic gastritis was a usual finding in both the non-operated and operated DU patients. Marked differences in the gastric body mucosa are seen after vagotomy compared to the non-operated DU patients (publ. III). The prevalences of atrophic corpus gastritis in these two groups were 21% and 1% ($p<0.001$), of superficial gastritis 76% and 76%, and of normal corpus mucosa 3% and 23%, respectively ($p<0.001$). In the antral mucosa, gastritis was present in both operated and non-operated patients in almost all cases, the prevalences being 99% and 100%, respectively. There were no differences in the degrees of antral gastritis.

At the same time, from 63 after-vagotomy atrophic corpus gastritis cases 16 were moderate and 2 severe while there were

no advanced degrees of atrophy in the non-operated patients. Our results show that the gastric body mucosal state in the operated cases does not depend upon the type of vagotomy but rather on its completeness (publ. III). The prevalence of atrophic corpus gastritis is significantly ($p<0.01$) higher in the complete than in the incomplete vagotomy cases, 29% and 12%, respectively. On the other hand, superficial corpus gastritis is significantly lower in the complete than in the incomplete vagotomy group: 69% and 85%, respectively ($p<0.01$). It seems that after vagotomy the progression of corpus gastritis in DU patients with a relatively stable antral gastritis will grow similar to the gastritis of non-operated gastric ulcer patients with a long history (Maaroos et al., 1985). This idea, however, needs further study.

The development and progression of postvagotomy corpus gastritis has been reported in literature (Liavag and Vaage, 1972; Roland et al., 1975; Holle, 1978; Watt et al., 1983; Äärimaa et al., 1984; Aase et al., 1985). The reason for the development of atrophic changes after a successful vagotomy are not clear. It is possible that after vagotomy the markedly degenerated vagal branches observed in the corpus (Valentin et al., 1987) lead to cell atrophy via a decreased trophic effect of the vagal nerves (Argov et al., 1986). Some authors have found a decrease in the size and number of parietal cells shortly after PV (Liavag and Vaage, 1972; Roland et al., 1975). Äärimaa et al. (1984) have reported also an increase of round cell infiltration in association with the decreasing amount of parietal cells. Results similar to those of the present study have been described earlier when the development of atrophic changes in the corpus mucosa 2–3 years after PV was discussed (Jonsson et al., 1988).

One of the contributing factors for the development of postvagotomy corpus gastritis may be the behaviour of the HP infection in this process.

4. Long-term effect of vagotomy on frequency and density of Helicobacter pylori colonisation.

In similarity to the morphological findings, the HP colonisation of the antral and corpus mucosa appears rather independent of the type of vagotomy performed. However, there is a difference in the frequency and density of HP infestation depending on the success of vagotomy. Our data show for

the first time that during a long-term period vagotomy causes a significant decrease of HP frequency in the antrum and increase in the body (publ. III). In the antral mucosa HP frequency was significantly ($p<0.001$) lower in the complete (75%) than in the incomplete vagotomy cases (94%) and in the non-operated group (93%) ($p<0.001$). In the body mucosa there were no significant differences in HP frequencies between the complete and incomplete vagotomy groups, 85% and 91%, respectively. However, both of these values are significantly higher than in the non-operated DU patients (71%) ($p<0.01$). Our results show that HP infestation is mainly associated with signs of superficial inflammation. After vagotomy superficial gastritis in the antrum was observed in 92% and in the corpus in 76% of cases. HP was present in 86% and in 90% of cases, correspondingly. The respective percentage of HP colonization for non-operate DU patients were 93% and 78%.

HP occurs less frequently in atrophic gastritis, in the antrum in 75% and in the corpus in 76% of the cases. The respective percentages for non-operated DU patients were 100% and 50%.

The bacterial infestation was absent in all cases of morphologically normal antrum mucosa. In normal corpus mucosa of the operated patients HP was present in 76%, and of non-operated patients in 66% of the cases.

The present study confirms that both HP and antral gastritis are connected with peptic ulcer (Price et al., 1985; Graham, 1989) as is the case in general population (Maaroos et al., 1990). At that Wyatt et al., 1987, suggest that the presence of gastric metaplasia in the duodenum induced by gastric acid in DU patients allows these bacteria to colonize the duodenum. It means that both the acid and HP infection are necessary for the development of DU and the elimination of either of them would be expected to result in healing. During a longer after-vagotomy period the development of recurrent ulcers may be avoided by the combination of a reduction of gastric acidity leading to a considerable decrease of gastric metaplasia in the duodenum (Wyatt et al., 1987) on the one hand, and by a marked decline of HP in the antrum and evidently by that way in the duodenum as well, on the other. According to this study, these are the results guaranteed by a complete vagotomy. In our series 5–12 years after a successful operation (complete vagotomy without ulcer recurrence) the HP colonisation was

significantly decreased in the antrum while it had increased in the corpus, when compared to nonoperated DU patients. However, it is important to note that in most cases HP colonization persists both in the antrum and the corpus, in 75% and 85%, respectively. It follows from here that during a long period the effectiveness of complete vagotomy in the treatment of DU diseases both after PV and TV is connected mainly with the reduced gastric acidity but not with the HP colonization changes in the stomach. Obviously reduced gastric acidity leads to the disappearence of gastric metaplasia in the duodenal bulb, as has been shown earlier after PV (Wyatt et al., 1987), hence, the aggressive effect of HP colonization in the duodenal bulb is ruled out.

Complete vagotomy lowers the effect of the acid-peptic factors (Barth, 1980), may interfere with the prostaglandin synthesis (Barth, 1980), changes the composition of mucus (Brückner et al., 1980), and leads to motor disturbances and other alterations that might create unfavourable conditions for the survival of the bacteria, as shown in this study.

In our material after vagotomy HP colonization increased in the corpus mucosa, but in addition, the prevalence of HP infestation was significantly lower in the cases with corpus atrophy than in those with superficial corpus gastritis (publ. III). It is possible that HP may act as a trigger in the initiation process and may further enhance the progression of gastritis in the corpus mucosa after vagotomy in DU patients (Sipponen et al., 1988). Accordingly, as observed in this study, the development of atrophic changes can be related to HP infestation. This view is further supported by follow-up studies with suggest that HP infestation is mainly related to the early phases of gastritis processes and that its significance decreases in the atrophic phase of chronic gastritis (Siurala et al., 1988; Maaroos et al., 1990).

On the background of the decrease of HP frequency in the antrum and increase in the body, in both parts of the stomach a significant rise of HP intensity occurs, compared to the non-operated DU patients (publ. III). HP high grade cases were for 19% more frequent in the antrum and 31% more frequent in the gastric corpus than in the non-operated DU cases. A peculiar finding was the increase of HP intensity which was higher after incomplete than complete vagotomy. The difference was signifi-

cant in the antrum but not in the body. On the other hand, the number of subjects with a high grade HP colonization in the corpus mucosa was significantly ($p<0.001$) higher in the complete vagotomy than in the non-operated group, 40% and 13%, respectively, while no difference was found in this respect with regard to the antral mucosa.

It has been reported that in peptic ulcer patients the antral mucosa has a much better potential for immunological defence than the body mucosa (Valnes et al., 1984). It is probable that the after-vagotomy changes of HP intensity observed in this study reflect the local changes of the immunological state of the gastric mucosa (Wyatt et al., 1986). How vagotomy influences the immunological state of gastric mucosa and which are its associations with the mucosal and HP colonisation changes described in this study, needs further clarification.

Part IV
Evaluation of postvagotomy ulcer recurrence risk: endoscopic Congo Red test, gastric acid secretion tests, serum pepsinogen I and Helicobacter pylori

Numerous reasons for recurrent ulcer development after vagotomy have been pointed out (Becker and Caspary, 1980; Amdrup, 1981; Feifel and Koller, 1982; Muller and Martinoli, 1985; Siewert and Hölscher, 1986): incompleteness of vagotomy, either due to the surgical technique and/or the constitutional peculiarities of the patient; reinnervation after vagotomy; disturbances of gastric emptying; improper method of the operation; smoking and consumption of alcohol; rise in gastrin after vagotomy; hypergastrinemy due to gastrin cell hyperplasia in the antrum, or the Zollinger-Ellison syndrome; other hormonal disturbances like hyperparathyroidism. Out of these, the most frequent cause still is the incompleteness of vagotomy (Adami et al., 1984; Siewert and Hölscher, 1986).

There is no generally accepted policy in the estimation of recurrent ulcer risk after vagotomy.

To estimate the risk for postvagotomy recurrent ulcer, mainly three methods can be used. The earliest of these three employs different gastric acid secretion parameters and so necessitates gastric probing, and is therefore timeconsuming

and distressing for the patient. The later methods for estimating the risk include ECRT and S–PG I. ECRT is performed during gastroscopy and provides a picture of mucosal changes in the esophagus, stomach and upper duodenum, particularly of recurrent ulcer.

Post-vagotomy endoscopy is essential since a certain proportion of ulcer relapses are asymptomatic. This has been shown both in our series and in literature (Muller and Martinoli, 1985; Raab et al., 1989). The present study shows that besides ECRT BAO>1.5 mmol/h + NAO>30 mmol/12h have a good discriminatory ability for ulcer recurrence prognosis, with a sensitivity of 80% and specifity of 81% (Table 6).

Table 6

Sensitivity and specifity of secretory tests in discrimination of patients with recurrent ulcer after vagotomy

Laboratory test	Sensitivity	Specifity
S–PG I>100 μg/l	69 %	46 %
S–PG I>150 μg/l	54 %	92 %
BAO>1.5 mmol/h	73 %	74 %
MAO>10 mmol/h	55 %	84 %
NAO>10 mmol/h	73 %	59 %
BAO>1.5 mmol/h + NAO>30 mmol/12h	80 %	81 %
Insulin test	83 %	78 %

It follows from here that at values below these combinations the development of recurrent ulcer is unlikely. According to data in the literature, ulcer recurrence rates do not depend significantly on whether the acid secretion remains high immediately after vagotomy or whether there is an early low secretory output that increases over time (Butterfield et al., 1982). It means that to estimate the recurrence ulcer risk, repeated BAO and NAO may prove necessary for determining the gastric acid secretion level

and its rise during the follow-up period. In practice, however, the use of these tests is limited because they are distressing for the patient.

In our series, the insulin test also showed a relatively high sensitivity and specifity for recurrent ulcer risk, 83% and 78%, respectively (Table 6). In other series 5 years after proximal vagotomy (Lunde et al., 1983), the sensitivity of the insulin test was 87%, whereas its specifity was only 52%, so reducing considerably the value of the test for recurrent ulcer prognosis. In addition, the insulin test is most difficult for the patient to endure and may lead to complications (Feifel et al., 1974). That is why it has been advised to avoid using this test.

The sensitivity and specifity of other gastric acid secretion parameters in the discrimination of postvagotomy recurrent ulcer is lower (Table 6). This view is supported by data in the literature (Graffner et al., 1986) although recurrent ulcer patients have higher mean BAO and MAO values than those without ulcer relapses (Graffner et al., 1986; Macintyre et al., 1990) as confirmed also by our data (publ. VI).

The essential finding in our study was the reliability of ECRT results in prognosing recurrent ulcer risk 5–12 years after vagotomy. ECRT is primarily characteristic of vagally controlled gastric secretion (Saik, 1983; Donahue et al., 1986). In our series nearly all (18/19) recurrent ulcer patients were ECRT positive, showing that postvagotomy recurrent ulcer risk is connected with the residual vagal innervation in the gastric corpus. It means that incompleteness of vagotomy and its role in the development of recurrent ulcer after the operation still remain the central problems, as has been shown earlier (Siewert and Hölscher, 1986).

From our material a conclusion of high practical importance can be drawn: In negative ECRT there is a 95% probability for excluding the risk of ulcer recurrence after vagotomy. This conclusion is based on our series where 18 (95%) recurrent ulcer cases out of 19 were ECRT positive and only 1 case (5%) was negative. It means that in case of a complete vagotomy (negative ECRT) no further ulcer risk studies are necessary. In ECRT positive cases, however, the specifity of the test for prognosing recurrent ulcer is low (53%), so in ECRT positive cases we need further studies for estimating the ulcer relapse risk.

A simple and relatively non-invasive method for the patient

is S–PG I that correlates with basal and stimulated output of pepsinogen secreted into the gastric lumen (Waldum et al., 1978). It has been reported earlier that in non-operated DU patients, for clinical purposes, S–PG I is not useful for evaluating the "severity" of duodenal ulcer (Samloff and Taggart, 1987). Still, high S–PG I values have been helpful in selecting patients to receive maintenance therapy for recurrence prophylaxis (Sumii et al., 1989).

In our series 5–12 years after vagotomy the mean S–PG I in patients with recurrent ulcer was significantly higher than in patients without recurrence (publ. VI) as has also been reported earlier (Stabile et al., 1978). Table 6 shows that a S–PG I > 150 μg/l was the most specific (92%) means for detecting ulcer relapses, but the sensitivity of this finding is low (54%). Our series demonstrate that in the development of ulcer recurrences the sensitivity of high S–PG I > 150 μg/l increases up to 100% when ECRT is positive. In ECRT negative cases high S–PG I values were not decisive in this respect (Fig. 3).

Earlier it has been shown that there is no correlation between BAO and S–PG I (publ. II), and PAO and S–PG I (Feldmann et al., 1988), neither before nor after vagotomy.

We found a significant positive correlation between S–PG I and NAO values in patients with recurrent ulcer ($r=0.806$, $p=0.015$) while such correlation was absent in other patients. It means that after vagotomy there is some correlation between higher acid values and higher S–PG I values whereas there is no such correlation in case of lower values. Therefore, both gastric acid secretion and S–PG I have to be considered together in order to prognose postvagotomy ulcer recurrence.

Up to now, there is no data concerning the changes of HP colonization after vagotomy during a longer term. It is known, however, that the eradication of HP infestation results in a long-lasting prevention of ulcer recurrence in non-operated DU patients (Marshall et al., 1988; Rauws and Tytgat, 1990). Our study shows in a fairly large material that in long-term period after complete vagotomy, without recurrent ulcer, HP colonization in the antrum decreases and in the corpus mucosa increases. Still, in 75% of the patients HP colonization persisted in the antrum and in 85% in the corpus after complete vagotomy according to ECRT. In cases of incomplete vagotomy, including those with ulcer recurrences, however, HP colonization persist-

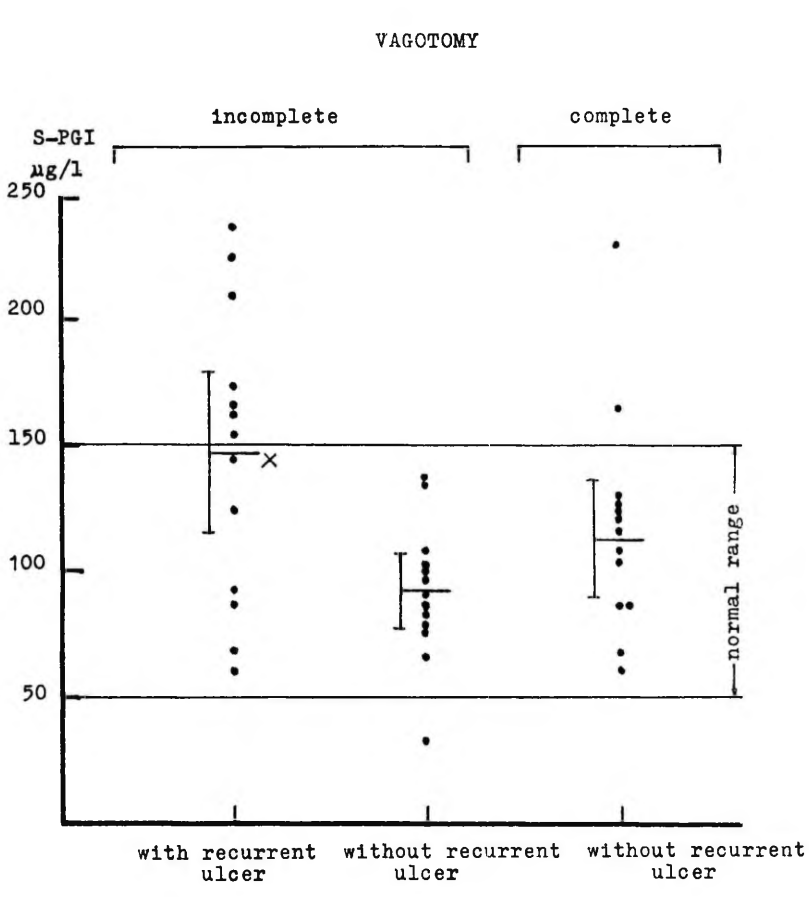

Fig. 3. Distribution and mean±SE of S–PG I in incomplete vagotomy (with and without recurrent ulcer) and complete vagotomy (without recurrent ulcer) groups 5–12 years after operation in DU patients. In incomplete vagotomy group: *p<0.05 recurrent ulcer versus without recurrence.

ed in the antrum in 94% and in the corpus in 91% of cases. At that the intensity of HP colonization in the incomplete vagotomy cases both in the antrum and in the corpus mucosa was higher than in the complete vagotomy cases and even more higher compared to the non-operated DU patients (publ. III). The above-said suggests that the persistance of HP infestation and a rise in its intensity in the antrum and in the corpus mucosa of incomplete vs. complete vagotomy can be a contributing factor for the development of recurrent ulcer only on the background of a relatively high gastric acidity.

It has been shown earlier that in addition to the presence of HP infestation, the intensity of it also plays a role as a risk factor in the pathogenesis of peptic ulcer disease (Stolte et al., 1989; Maaroos et al., 1991). There are no data about such a rise in HP colonisation intensity after vagotomy according to our results. It remains to be shown by future research which is the role of a high intensity HP colonisation in the antrum and corpus in the development of recurrent ulcer in these patients who had not yet developed a recurrence during 5–12 years on the background of incomplete vagotomy according to ECRT in this material, and whether HP eradication will lead to the prevention of recurrent ulcer.

Analysing the results of the different methods, one can see that no one single method exists that is both of high sensitivity and of high specifity for estimating the recurrent ulcer risk and at the same time is easy for the patient: Hence, these methods have to be combined. The present study shows that it is expedient to start with ECRT. It is a relatively quick and high-sensitive method. If ECRT is negative, the development of recurrent ulcer is unlikely in 95% of cases and no further studies along those lines are needed. If ECRT is positive, the next step is to determine S–PG I which is easier for the patient than quantitative acid measurements. In high S–PG I cases there exists a high risk for ulcer relapse. Repeated S–PG I during the follow-up period for detecting patients with recurrent ulcer risk will make it possible to avoid relapses by a timely preventive therapy. At the same time, the determination of quantitative acid data like BAO in combination with NAO is necessary in certain cases in order to evaluate the risk of ulcer relapse and for finding out the real causes of recurrent ulcer and planning its further treatment.

Conclusions

1. Our study shows that endoscopic Congo Red test is more sensitive and relevant for clinical purposes in order to predict the completeness of vagotomy than multiple criterial insulin test and nocturnal acid output reduction test are.
2. According to endoscopic Congo Red test, in a long-term period after the operation incomplete vagotomy is considerably more frequent after proximal (56%) than after truncal vagotomy (34%). The areas of incomplete vagotomy were predominantly located in the upper part of the corpus mucosa: 82% of the cases after proximal vagotomy and even more after truncal vagotomy.
3. In general, vagotomy does not decrease the serum pepsinogen I level during the operation either locally in the gastric corpus veins or in the peripheral venous blood. Still, during the first postoperative year vagotomy causes a significant and continuous decrease of mean serum pepsinogen I but not in all individual cases, and much less than gastric acidity does. These changes do not depend on the type of vagotomy.
4. In a long-term period after the operation, the levels of serum pepsinogen I do not depend on the completeness of vagotomy and therefore the levels of serum pepsinogen I cannot serve as an indicator for the completeness of vagotomy.
5. The effect of vagotomy on the gastric mucosa and Helicobacter pylori colonization 5–12 years after the operation depends on the completeness but not on the type of vagotomy.

   Vagotomy causes: considerable atrophic changes in the gastric corpus mucosa which are more pronounced after complete than incomplete vagotomy; a decrease in the frequency of Helicobacter pylori colonization in the antral mucosa that is more significant in complete vagotomy cases, and an increase in Helicobacter pylori colonization frequency in the gastric corpus mucosa; an increase in the intensity of Helicobacter pylori colonization both in the antrum and in the corpus mucosa which is more considerable after incomplete vagotomy.
6. Recurrent ulcer in a long-term period after vagotomy is

characterized by incompleteness of vagotomy according to endoscopic Congo Red test. Ulcers develop more often in cases of large incomplete vagotomy areas involving 20% or more of the gastric corpus mucosa; higher mean values of basal acid output, nocturnal acid output, serum pepsinogen I and in most cases a high intensity Helicobacter pylori colonization in the antrum and corpus mucosa.

7. For prognosing the postvagotomy recurrent ulcer risk endoscopic Congo Red test should be made first. In negative endoscopic Congo Red test cases the development of recurrent ulcer is unlikely. In case of a positive endoscopic Congo Red test the determination of levels of serum pepsinogen I or basal acid output in combination with nocturnal acid output is necessary for the ulcer risk prognosis.

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References

Aase S, Roland M, Liavåg I et al. Stereological analysis of human parietal cell, before and 6 months after vagotomy // Scand J Gastroenterol 1985, 20, 257–267

Äärimaa M, Härkönen M, Varis et al. Serum group I pepsinogens during insulin and pentagastrin tests in unoperated and vagotomized duodenal ulcer patients // Scand J Gastroenterol 1987, 22, 956–960

Äärimaa M, Söderström K-O, Kalimo H et al. Morphology and function of the parietal cells after proximal selective vagotomy in duodenal ulcer patients // Scand J Gastroenterol 1984, 19, 787–797

Adami HO, Enander LK, Enskog L et al. Recurrences 1 to 10 years after highly selective vagotomy in prepyloric and duodenal ulcer disease // Ann Surg 1984, 199, 393–399

Amdrup E. Recurrent ulcer // Br J Surg 1981, 68, 679–680

Argov S, Herschlag A, Mordovich D. What happens to the parietal cell following truncal vagotomy? // World J Surg 1986, 10, 450–453

Bank S, Marks JN, Louw JH. Histamine-and-insulin-stimulated gastric acid secretion after selective and truncal vagotomy // Gut 1967, 8, 36–41

Baron JH. Clinical tests of Gastric secretion. History, methodology and interpretation. Great Britain. Unwin Brothers Limited 1978

Barth H. Hypothesen zur Bedeutung des Histamins und Prostaglandine in der Ulcus pathogenese // Nichtresezierende Ulcuschirurgie, Berlin, Heidelberg, New York. Springer-Verlag 1980, 9–19

Bateston M, Bouchier J. Clinical investigation of gastrointestinal function. Oxford, London, Edinburgh, Boston, Melbourne. Blackwell Scientific Publications 1981

Becker HD, Caspary WF. Postgastrectomy and postvagotomy syndroms. Berlin (West) – Heidelberg – New York. Springer-Verlag 1980

Bell BF, Battersby K. Effect of vagotomy on gastric mucosal blood flow // Gastroenterology 1968, 54, 1032–1036

Blackett RL, Johnston D. Recurrent ulceration after highly selective vagotomy for duodenal ulcer // Br J Surg 1981, 68, 705–710

Blazer MI. Gastric Campylobacter-like organisms, gastritis and peptic ulceration // Gastroenterology 1987, 93, 371–383

Braghetto T, Csendes A, Lazo M et al. A prospective randomized study comparing highly selective vagotomy and extended highly selective vagotomy in patients with duodenal ulcer // Amer J Surg 1988, 155, 212–218

Brückner W, Heltzel W, Kleinschmidt I. Pepsin-, Intrinsic-Factor und Schleim Secretion nach PV und Pyloroplastic // Nichtresezierende Ulkuschirurgie. Berlin, Heidelberg, New York. Springer-Verlag 1980, 185–191

Butterfield DI, Whitfield PF, Hobsley M. Changes in gastric secretion with time after vagotomy and the relationship to recurrent duodenal ulcer // Gut 1982, 23, 1055–1059

Cheli K, Gjacosa A. Duodenal ulcer and chronic gastritis. Endoscopy 1986, 18, 125–126

Clark CG, Murray IG. The Burge test for complete vagotomy // IR Coll Surg Edinburgh 1963, 8, 212–218

Coghlan JG, Gilligan D, Humphries H et al. Campylobacter pylori and recurrence of duodenal ulcers – a 12 months follow-up // Lancet 1987, 11, 1109–1111

Cox HT, Poller L, Thomson IM. Gastric fibrinolysis: A possible aetiological link with peptic ulcer // Lancet 1967, 1, 1300–1302

Debas HT. Proximal gastric vagotomy interferes with a fundic inhibitory mechanism // Amer J Surg 1983, 146, 51–56

Dewar EP, Dixon MF, Johnston D. Bile reflux and degree of gastritis after highly selective vagotomy, truncal vagotomy and partial gastrectomy for duodenal ulcer // World J Surg 1983, 7, 743–750

Donahue PE, Bombeck TC, Yoshida I et al. Endoscopic Congo Red Test during proximal gastric vagotomy // Amer J Surg 1987, 153, 249–255

Donahue PE, Bombeck TC, Yoshida I et al. The simplified Endoscopic Congo Red Test for completeness of vagotomy // Surg Gynecol Obstet 1986, 163, 287–298

Donahue PE, Maroske D. Rocher DH et al. Experience with the endoscopic test for completeness of vagotomy. Results of application in two medical centers // Zenbl Chir 1987, 112, 1208–1215

Drapanas T, Woolverton WC, Reeder IW et al. Experience with surgical management of acute gastric mucosal hemorrhage.

A unified concept in the pathophysiology // Ann Surg 1971, 173, 638–640

Dragstedt LR, Harper PV, Tovee EB et al. Section of vagus nerves to the stomach in the treatment of peptic ulcer, complications and end results after 4 years // Ann Surg 1947, 126, 687–708

Faber RG, Russell RCT, Parkin IV et al. The predictive accuracy of the postvagotomy insulin test. A new interpretation // Gut 1975, 16, 337–342

Feifel G, Falkenberg P, Kemkes B et al. Die Problematik des Insulin-Tests als postoperative Vagotomie Kontrolle. Münch Med Wsch 1974, 116, 995–1000

Feifel G, Koller H. Das Ulcus Rezidiv nach chirurgischer Therapie des Ulcus Duodeni // Chirurg 1982, 53, 23–28

Feldman M, Blair AI, Richardson CT et al. Effect of proximal gastric vagotomy on serum pepsinogen I and II concentrations and acid secretion in duodenal ulcer patients // Dig Dis Sci 1988, 33, 824–827

Feldman M, Richardson CT, Lam SK et al. Comparison of gastric acid secretion rates and serum pepsinogen I and II concentrations in occidental and oriental duodenal ulcer patients // Gastroenterology 1988, 95, 630–635

Gallinger JU, Nikolajeva TL, Darenskaja SD. Postoperative estimation of the postoperative completeness of vagotomy according to Endoscopic Congo Red Test // Surgical treatment of the ulcer disease. Moscow, 1979, 114–117 (in Russian)

Goedhard JG, Biemond I, Giliams JP et al. Serum pepsinogen I levels: assessment of gastric acid secretion? In: Kreuning J, Samloff IM, Rotter JI, Eriksson AW. Pepsinogens in man. clinical and genetic advances. Alan R Liss, New York, 1985 (Prog Clin Biol Res, 173), 139–146

Goligher JC. A technique for highly selective (parietal cell or proximal gastric) vagotomy for duodenal ulcer // Br J Surg 1974, 61, 337–345

Goodwin CS, Amstrong IA, Marshall BI. Campylobacter pyloridis, gastritis and peptic ulceration // J Clin Path 1986, 39, 353–365

Cowley DI, Spencer I, Baron IH. Acid secretion in relation to recurrence of duodenal ulcer after vagotomy and drainage // Br J Surg 1973, 60, 517–522

Graffner H, Lindberg G, Oscarson J. Acid Secretory Tests in peptic ulcer disease before and after parietal cell vagotomy // Scand J Gastroenterol 1986, 21, 41–46

Graham DY. Campylobacter pylori and peptic ulcer disease // Gastroenterology 1989, 96, 615–625

Grassi G, Orecchia C. A comparison of intraoperative tests of completeness of vagal section // Surg 1974, 75, 2, 155–160

Greenall MI, Lyndon PJ, Goligher J et al. Long-term effects of highly selective vagotomy on basal acid and maximal acid output in men // Gastroenterology 1975, 68, 1421–1429

Hallenbeck GA, Gleysteen II, Aldrete IS et al. Proximal gastric vagotomy: effect of two operative techniques on clinical and gastric secretory results // Ann Surg 1976, 184, 435–442

Hamilton J, O'Connor HJ, Wood NC et al. Healing and recurrence of duodenal ulcer after treatment with tripotassium dicitrate bismuthate (TDB) tablets or cimetidine // Gut 1986, 27, 106–110

Haukland HH, Waldum HL, Johnston JA. Effect of proximal gastric vagotomy on insulin-included gastric H^+ and pepsin secretion and serum group I pepsinogens // Scand J Gastroenterol 1982, 17, 555–559

Hildebrandt J, Lauschke G, Wolff H et al. Selective proximale Vagotomie mit und ohne Pyloroplastik – Ergebnisse einer randomisierten klinischen Studie nach 5 und 8 Jahren beim Ulcus duodeni // Zenbl Chir 1988, 113, 827–836

Hodge AI, Masarei IR, Catchpole BN. The role of the sympathetic nervous system in hypoglycemia-stimulated gastrin secretion // Gut 1972, 13, 341–345

Hoffman I, Jensen H-E, Christiansen J et al. Prospective controlled vagotomy trial for duodenal ulcer. Results after 11–15 years // Ann Surg 1989, 209, 1, 40–45

Hollander F. The insulin test for the presence of intact nerves fibres after vagal operations for peptic ulcer // Gastroenterology 1946, 7, 607–614

Hollander F. Laboratory procedures in the study of vagotomy with particular reference to the insulin test. Gastroenterology 1948, 11, 419–425

Holle GE. Langzeituntersuchungen der Fundurschleimhaut beim Gastroduodenal ulkus nach SpV anu Pyloroplastic // Z Gastroenterol 1978, 16, 57–65

Holle GE, Frey KW, Thieme Ch et al. Recurrence of peptic ulcer after selective proximal vagotomy and pyloroplasty in relation to changes in clinical signs and symptoms between 1969 and 1983 // Surg Gynecol Obstet 1988, 167, 4, 271–281

Holst-Christensen J, Hansen OH, Pedersen T et al. Recurrent ulcer after proximal gastric vagotomy for duodenal ulcer // Br J Surg 1977, 64, 1, 42–46

Hood JM, Spencer FF, Macrae KD et al. Predictivate value of perioperative gastric acid tests // Gut 1976, 17, 998–1000

Jensen HE, Kjaergaard J, Meisner S. Ulcer recurrence two to twelve years after parietal cell vagotomy for duodenal ulcer // Surg 1983, 94, 802–806

Joffe SN, Crochett A, Doyle D. Morphologic and functional evidence of reinnervation of the gastric parietal cell mass after parietal cell vagotomy // Amer J Surg 1982, 143, 80–85

John DJB, McDermott FT. Influence at achlorhydria on aspirin-included occult gastrointestraal blood loss: studies on pernicious anaemia // Br Med J 1970, 2, 450–452

Johnson AG. The Contribution of the Grassi Intraoperative Test to the Technique of Vagotomy // Int Surgery 1980, 65, 4, 297–299

Johnston D. Selective-proximale Vagotomie mit ulkus exzision beim Ulcus Ventriceili. Magenchirurgie. Berlin, Heidelberg, New York, Tokyo Springer-Verlag. 1986, 167–175

Johnston D, Goligher JC. The influence of the individual surgeon and of the type of vagotomy upon the insulin test after vagotomy // Gut 1971, 12, 963–962

Johnston D, Thomas DG, Checketts RG et al. An assessment of postoperative testing for completeness of vagotomy // Br J Surg 1967, 54, 831–833

Jönsson K-A, Ström M, Bodemar G et al. Histologic changes in the gastroduodenal mucosa after long-term medical treatment with cimetidine or parietal cell vagotomy in patients with juxtapyloric ulcer disease // Scand J Gastroenterol 1988, 13, 433–441

Jordan PH Jr. Current status of parietal cell vagotomy // Ann Surg 1976, 184, 659–671

Jordan PH Jr, Condon RF. A prospective evaluation of vagotomy-pyloroplasty and vagotomy-antrectomy for treatment of duodenal ulcer // Ann Surg 1970, 172, 547–563

Jordan PH Jr, Thornby I. Should it be parietal cell vagotomy or selective vagotomy-antrectomy for treatment of duodenal ulcer? // Ann Surg 1987, 205, 5, 572–590

Kate RW, Pals G, Donker AJM et al. Renal clearance of pepsinogen A (Pg A) in healthy volunteers // Gastroenterol ogy 1986, 90, 5, 1660

Kekki M, Sipponen P, Siurala M. Progression of antral and body gastritis in patients with active and healed duodenal ulcer and duodenitis // Scand J Gastroenterol 1984, 19, 382–388

Kekki M, Siurala M, Varis K et al. Classification principles and genetics of chronic gastritis // Scand J Gastroenterol 1987, 22 (suppl 141), 1–28

Kjaergaard I, Jensen H-E, Allesmand H. Inadequately reduced acid secretion after vagotomy for duodenal ulcer // Ann Surg 1980, 192, IV 6, 711–715

Kronborg O. The short term stability of the insulin test after truncal and selective vagotomy for duodenal ulcer // Scand J Gastroenterol 1972, 7, 604–613

Kusakari K, Nyhus LM, Gillison EW et al. An endoscopic test for completeness of vagotomy // Arch Surg 1972, 105, 386–391

Kuzin MI, Postolov PM. Selective proximal vagotomy in the treatment of duodenal ulcer. World J Surg 1980, 4, 347–351

Liavag L, Vaage S. The effect of vagotomy and pyloroplasty on the gastrointestinal mucosa of the rat // Scand J Gastroenterol 1972, 7, 23–27

Loeweneck H. Anatomische Grundlagen der selective proximalen vagotomie Nichtresezierende Ulkuschirurgie. Berlin Heidelberg New York, Springen-Verlag 1980, 165–167

Loup P, Chavami B, Mirkovitsch W et al. Failure of vagotomy in the treatment of duodenal ulcer: Explicable by intramural nerve fibres or regeneration? // Chir Gastroenterol 1977, 11, 81–84

Lunde O-Ch, Lievåg I, Roland M. Recurrent ulceration after proximal gastric vagotomy for duodenal ulcer // World J Surg 1983, 7, 751–756

Lygidakis NJ. Histologic changes after elective surgery for duodenal ulcer // Acta Chir Scand 1986, 152, 139–144

Lyndon PI, Greenall MI, Smith RB et al. Serial insulin tests over a five year period after highly selective vagotomy for duodenal ulcer // Gastroenterology 1975, 69, 1188–95

Lyndon PI, Walsh IA, Johnston D et al. Gastrin and acid outputs in response to meat extract after truncal, selective and highly selective vagotomy for duodenal ulcer // Gut 1974, 14, 10, 824

Maaroos H-I, Kekki M, Sipponen P et al. Grade of Helicobacter pylori colonization, chronic gastritis and relative risks of contracting high gastric ulcers: A seven-year follow-up // Scand J Gastroenterol 1991, 26 (suppl. 196), 65–72

Maaroos H–I, Kekki M, Villako K et al. The occurrance and extent of Helicobacter pylori colonization and antral and body gastritis profiles in an Estonian population sample // Scand J Gastroenterol 1990, 25, 1010–1017

Maaroos H-I, Salupere V, Uibo R et al. Seven-year follow-up study of chronic gastritis in gastric ulcer patients // Scand J Gastroenterol 1985, 20, 198–204

Macintyre IMC, Millar A, Smith AN et al. Highly selective vegotomy 5–15 years on // Br J Surg 1990, 77, 65–69

Marshall BI, Goodwin CS, Warren JK et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori // Lancet 1988, 2, 1437–1442

Mason N, Giles G, Graham N et al. An early assessment of selective and total vagotomy // Brit J Surg 1968, 55, 677–680

Muller C, Martinoli S. Die proximale selective Vagotomie in der Behandlung der gastroduodenalen Ulkuskrankheit. Berlin (West) Heidelberg New-York Tokyo, Springer-Verlag 1985

Nylamo EJ. Relationship between gastric acid secretion and clinical outcome after parietal cell vagotomy // Acta Chir Scand 1987, 153, 33–36

O'Connor HI, Dixon MF, Wyatt JJ et al. Effect of duodenal surgery and enterogastric reflux on Campylobacter pylori // Lancet 1986, ii, 1178–1181

Paimela H, Ahonen J, Höckerstedt K et al. Five-year results of proximal gastric vagotomy // Ann Chir Gynaec 1983, 72, 3–8

Paimela H, Lalla M, Räsanen V. Serum group I pepsinogens after consecutive stimulations with insulin and pentagastrin

in unoperated duodenal ulcer patients and in duodenal ulcer patients after proximal gastric vagotomy // Scand J Gastroenterol 1984, 19, 52–55

Peetsalu A. Blood coagulation changes in gastric or duodenal ulcer and in hemorrhages caused by them. Soviet Estonian Health 1972, 6, 514–516 (in Estonian)

Peetsalu A, Peetsalu M, Väli T et al. Long-term results after truncal vagotomy with ulcer excision and pyloroplasty Holle in the treatment of pyloro-duodenal ulcer. Medical theory and practice. Tartu, 1990, 49–50 (in Estonian)

Petkaneshkov G, Mitova K, Michova A et al. Effect of PGV and PGV with pyloroplasty on gastric colonization with campylobacter-like organisms // The World Congress of gastroenterology, Sydney, Australia, 16–31 August 1990, Abstracts II PD 96

Plebani M, Di Mario F, Vianello F et al. Actual role of pepsinogen group I in the study of upper gastrointestinal diseases // Clin Biochem 1983, 16, 310–312

Price A, Levi I, Dolby IM et al. Campylobacter pyloridis in peptic ulcer disease: Microbiology, pathology and scanning electron microscopy // Gut 1985, 26, 1183–1188

Raab M, Said S, Hilgers RD et al. Long-term results of highly selective vagotomy for the treatment of duodenal ulcer // Hepatogastroenterol 1989, 36, 357–362

Raab M, Stützer R. Die selektiv proximale Vagotomie zur Behandlung der Ulcus duodeni // Langenbeck Arch Chir 1986, 368, 41–55

Rauws EAI, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of H. pylori // Lancet 1990, 225, 1233–1235

Reisig JH, Vinz H, Georgi W. Revisionsoperationen nach Vagotomie // Zenbl Chir 1985, 110, 505–523

Roland M, Berstad A. Liavag I. Histological study of gastric mucosa before and after proximal gastric vagotomy in duodenal ulcer patients // Scand J Gastroenterol 1975, 10, 181–186

Rosati J, Serantoni C, Ciani PA. Extended selective proximal vagotomy: observation of a variant technique // Surg Gastroenterol 1976, 10, 33–37

Saik RP, Geenburg AG, Farris JM et al. The practicality of the Congo Red test or is your vagotomy complete? // Amer J Surg 1976, 132, 144–149

Saik PR, Greenburg AG, Peskin GW. The Congo Red Test to determine completeness of vagotomy // Amer J Surg 1982, 144, 518–522

Saik PR. Vagotomy testing. New York: Futura Publishing CO., INC MOUNT Kisco, 1983

Samloff JM, Secrist DM, Passaro E. Serum group I pepsinogen levels and their relation to gastric acid secretion in patients with and without recurrent ulcer // Gastroenterology 1976, 70, 309–313

Samloff JM, Taggart RM. Pepsinogens, pepsins and peptic ulcer // Clin Invest Med 1987, 10, 3, 215–221

Schreiber HW, Schumpelick V. Selektiveproximale Vagotomie mit ösophagealer und ventrikulärer Myotomie. Magenchirurgie. Berlin, Heidelberg, New York, Tokio, Springer-Verlag, 1986, 176–178

Sibul U. Proximal Vagotomiy. Tallinn, "Valgus" 1985

Siewert IR, Hölscher AH. 20 Jahre vagotomie: Indikationen und Verfahrenswahl-ulcus duodeni // Zenbl Chir 1986, 111, 913–966

Sipponen P, Seppälä K, Äärynen M et al. Chronic gastritis and gastroduodenal ulcer: A case control study or risk of coexisting duodenal or gastric ulcer in patients with gastritis // Gut 1989, 30, 922–929

Sipponen P, Valle J, Varis K et al. Fasting levels of serum gastrin in different morphologic states of the antrofundal mucosa: An analysis of 860 subjects // Scand J Gastroenterol 1990, 25, 513–519

Sipponen P, Varis K, Gederberg A et al. Campylobacter pylori is associated with chronic gastritis but not with active peptic ulcer disease // APMIS 1988, 96, 84–88

Siurala M, Sipponen P, Kekki K. Campylobacter pylori in sample of Finnish population: Relation to morphology and functions of the gastric mucosa // Gut 1988, 29, 909–915

Smith JS, Gillespie G, Elder JG et al. Time of conversion of insulin response after vagotomy // Gastroenterology 1972, 62, 912–917

Stabile BE, Passaro E Jr, Samloff JM et al. Serum pepsinogen I and gastric acid output in postoperative recurrent peptic ulcer // Arch Surg 1978, 113, 1136–1141

Staël von Holstein C, Graffner H, Oscarson J. One hundred patients ten years after partial cell vagotomy // Br J Surg 1987, 74, 101–103

Stempien SJ, Dagardi AE, Seifer HW. Status of duodenal ulcer patients five years or more after vagotomy-pyloroplasty // Proc. World Congress Gastroenterology (Washington) 1958, 1026–1034

Stolte M, Eidt S, Ritter M et al. Campylobacter pylori und Gastritis // Pathologe 1989, 10, 21–26

Sullivan RC, Wadell WR. Accumulated experience with vagotomy and pyloroplasty for surgical control of hemorrhagic gastritis // Amer J Surg 1968, 116, 745–748

Sumii K, Inbe A, Uemura N et al. Increased serum pepsinogen I and recurrence of duodenal ulcer // Scand J Gastroenterol 1989, 24, 1200–1204

Tamm A, Villako K, Härkönen H et al. Serum pepsinogen I and the state of gastric mucosa in an Estonian population sample // Scand J Gastroenterol 1984, 19, 1091–1094

Thompson JC, Lowder W, Peurifoy YT et al. Effect of selective proximal vagotomy and truncal vagotomy on gastric acid and serum gastrin responses to meal in duodenal ulcer patients // Ann Surg 1978, 188, 431–436

Valentin MAC, Domingues MD, Alonso MR et al. Vagal regulation after parietal cell vagotomy: An experimental study in dogs // World J Surg 1987, 11, 94–100

Valnes K, Brandtzay P, Elgjo H et al. Specific and non-specific humoral defence factors in the ephithelium of normal and inflamed gastric mucosa // Gastroenterology 1984, 86, 402–412

Vardja T, Peetsalu A, Peetsalu M. Long-term results after proximal vagotomy in the treatment of duodenal ulcer (5–11 years after operation). Actual problems in abdominal surgery and intensive care. Tartu, 1990, 20–21 (in Estonian)

Varis K, Raij K, Härkönen M et al. Cyclic AMP and gastric secretion in man // Scand J Gastroenterol 1988, 23, 1025–1034

Varis K, Salmi H, Cederberg A et al. Pepsinogenes in peptic ulcer disease and in non-ulcer dyspepsia // Hepatogastroenterol 1989, 36, 45

Vinz H, Reisig J, Klose P et al. Das Retsidivulkus nach selektiv proximaler Vagotomie // Z Klin Med 1988, 43, 1525–1530

Vuoristo M, Pikkarinen P, Samloff JM et al. Functional characteristics of duodenal ulcer patients and their first degree relatives // Scand J Gastroenterol 1991, 26 (suppl 186), 52–61

Waldum HL, Burhol PG, Straume BK. Serum group I pepsinogenes and gastrin in relation to gastric H^+ and pepsin outputs before and after subcutaneous injections of pentagastrin // Scand J Gastroenterol 1978, 13, 943–946

Waldum HL, Jorde R, Gunnes P. Renal excretion of and the effect of posture on serum group I pepsinogenes // Scand J Gastroenterol 1982, 17, 253–255

Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastrits // Lancet ii 1983, 1273–1275

Watt PSH, Sloan JM, Kennedy TL. Changes in gastric mucosa after vagotomy and gastrojejunostomy for duodenal ulcer // Br Med J 1983, 287, 1407–1410

Wyatt JJ, Rathbone BJ, Dixon MF et al. Campylobacter pylori and acid induced gastric metaplasia in the pathogenesis of duodenitis // J Clin Pathol 1987, 40, 841–848

Wyatt JJ, Rathbone RJ, Dixon MF et al. Local immune response to gastric campylobacter in non-ulcer dyspepsia // J Clin Pathol 1986, 39, 836–879

Yoshida J, Donahue PE, Polly EH et al. Pyloroplasty divides the efferent gastroepiploic vagus nerve // Gastroenterology 1988, 94, 5, 2, A–512

Publications

Acta et Commentationes Universitatis Tartuensis, 1989, 854.

CHANGES OF SERUM PEPSINOGEN I LEVEL IN PATIENTS WITH PEPTIC ULCER AFTER DIFFERENT GASTRIC OPERATIONS

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During the last decade several authors have dealt with the changes of serum pepsinogen I (Pg I) in operated and unoperated peptic ulcer patients /1-3/. The changes of the Pg I level are used to characterize the response of chief cells to various stimulators of gastric secretion as well as to different methods of operation. However, the authors do not agree about how closely serum Pg I and HCl secretion are connected with each other /4, 5/. The influence of the different types of vagotomy on PG I values has been examined in comparatively small groups of patients, and only during 1 - 3 months after the operation. The aim of the present report is to use more extensive material observing changes in serum Pg I before the operation and during one year after several variants of vagotomy and partial gastrectomy.

Material & Methods

82 patients with duodenal ulcer (DU) were studied, all of them operated on in the Department of Surgical Gastroenterology of the Tartu University Clinic in the yars 1981-1983. The male-female ratio was 74:8, the age of the patients - 10-72 years. In all of them the endoscopic diagnosis was confirmed at the operation. The choice of the surgical method depended on the value of the gastric secretion and the pathological findings in the stomach, pylorus and duodenum.

The operations were as follows: in 36 cases proximal vagotomy together with the excision of the ulcer and pyloroplasty (PV+P) was performed; 26 - proximal vagotomy (PV); in 14 - truncal vagotomy together the excision of the ulcer and pyloroplasty (TV+P); 6 - truncal

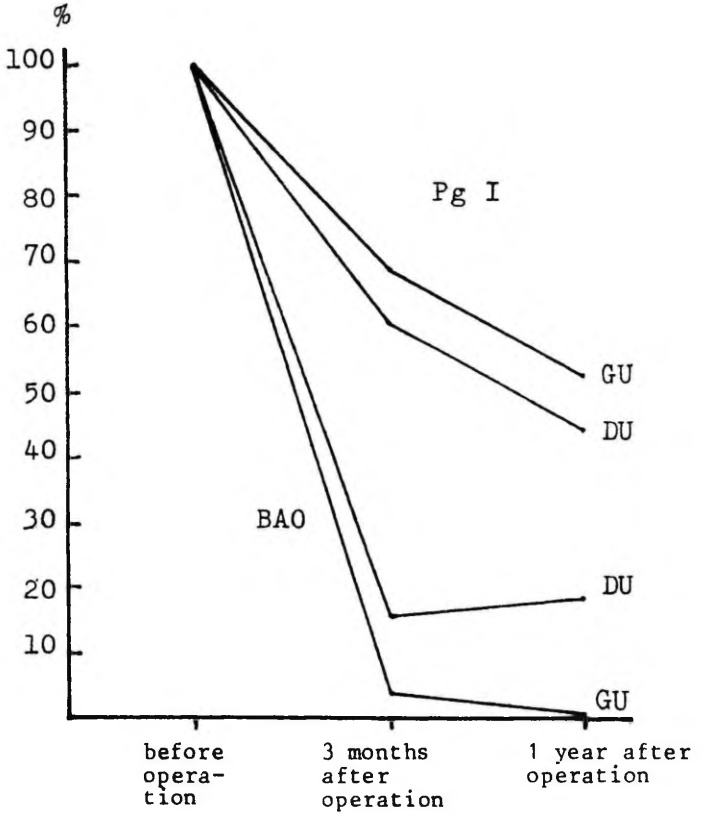


Figure 1. Average postoperative changes of BAO and Pg I values in duodenal ulcer (DU) and gastric ulcer (GU) patients

vagotomy with antrumectomy (TV+AE). The completeness et the vagotomy was checked by the Hollander test in 67 of DU patients.

For comparison the data of 11 patients with gastric ulcer (GU), operated on in the same department during the same period were used. They underwent Billroth I partial gastrectomy.

The blood sera from 82 DU and 11 GU patients were obtained on the morning prior to the collection of the gastric juice. The sera were stored at -20 °C until the determination of Pg I. The concentration of Pg I in the serum was determined in the Meilahti Hospital, in Helsinki, according to the radioimmunoassay method described earlier /6/. 44 subjects from adult population with no ulcer and with the normal fundal mucosa or superficial gastritis served as controls. The normal range for Pg I values was considered to be 50 - 150 µg/l /6/. In 64 patients Pg I values were determined 3 times (preoperatively, 3 months and 1 year postoperatively), and in 25 cases, accordingly, two times.

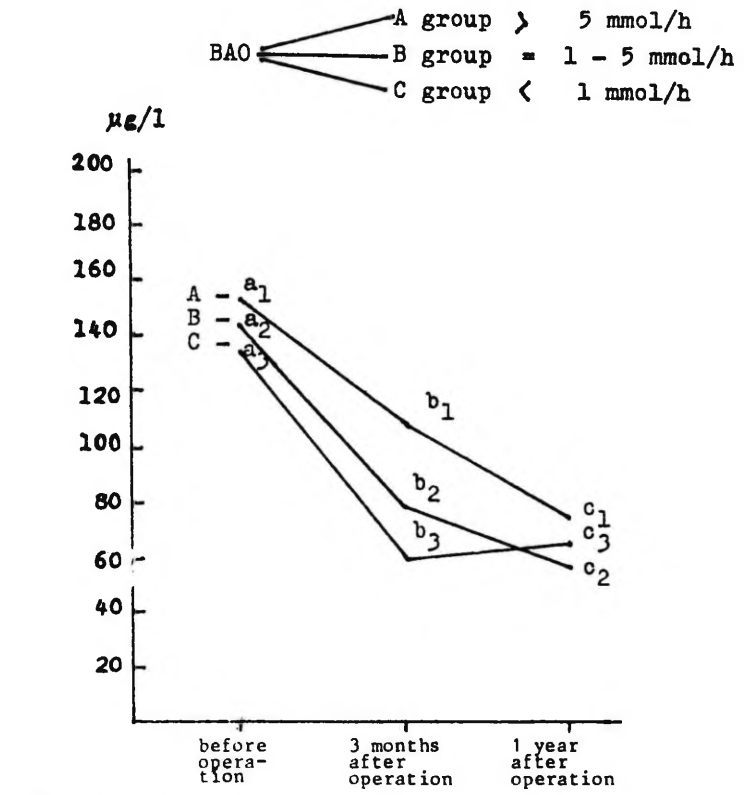
The gastric juice for determing the basal secretion (BAO) was collected during 60 minutes by continuous aspiration from the preliminarily emptied stomach. The position of the tube in the stomach was checked by X-rays. Normal BAO was 1 - 5 mmol/h. According to the BAO results the patients were divided into three groups: high (A), normal (B) and low (C).

In 39 DU patients gastroscopic biopsies were taken from the gastric body mucosa before the operation, and in 32 - after 1 year. The histological findings were classified by 5 stages, from normal mucosa (0), superficial gastritis (1) to severe atrophic gastritis (4) /7/.

In the statistical analysis the Student test for paired and unpaired data groups was used.

Results

Before the operation the gastric body mucosa was found be normal in 18 cases, in 21 superficial gastritis occurred. The serum Pg I concentration varied over a wide range from 50 - 404 µg/l. In the majority of the DU paitents (54 %) the PG I values were within the normal range. In 38 cases out of 82 (46 %) Pg I values were above 150 µg/l, in all (13 %) above 210 µg/l, which should be considered as particularly high.



$a_1 - a_2$ n.s.
$a_2 - a_3$ n.s.
$a_1 - a_3$ n.s.
$a_1 - b_1$ t = 3,3 p < 0,01
$a_1 - b_2$ t = 5,1 p < 0,001
$a_2 - b_3$ t = 2,7 p < 0,05

$b_1 - b_2$ n.s.
$b_1 - b_3$ t = 2,6 p < 0,05
$b_2 - b_3$ n.s.
$b_1 - c_1$ t = 2,8 p < 0,01
$b_2 - c_2$ t = 2,9 p < 0,01
$b_3 - c_3$ n.s.

$c_1 - c_2$ t = 2,5 p < 0,05
$c_1 - c_2$ n.s.
$c_2 - c_3$ n.s.

Figure 2. Postoperative Pg I changes according to the preoperative BAO level groups

High BAO was observed in 45 cases, normal in 29 cases and low in 6 DU patients. In 6 out of 10 GU patients BAO was normal, and in the remaining 4 cases lower than normal. The average preoperative value of BAO was significantly higher in DU patients ($p < 0.001$).

In all but one of the GU patients Pg I concentration was within normal limits, on average being significantly lower than in DU patients, respectively 97 ± 31 (mean ± SD) µg/l and 152 ± 67 µg/l ($p < 0.001$).

3 months and 1 year after the operation the average values of both BAO and Pg I decreased significantly, if compared to their preoperative levels (Fig. 1). 3 months later BAO had decreased by 85 % in DU patients and by 97 % in GU patients. There was no further decrease in DU cases, but it fell to a zero level in GU patients after the first postoperative year.

In the DU group Pg I decreased by 40 % in 3 months, and additional 16 % over 1 year after the operation. In DU patients the level of Pg I decreased altogether by 56 % during the first year ($p < 0.001$). The decrease in GU patients was respectively 32 % and 16 %, in total 48 % compared to the starting value ($p < 0.05$). Thus 3 months after the operation the decrease of the Pg I level was much less expressed than that of BAO. After one year the same picture persisted.

The Hollander test proved positive in 23 and negative in 44 cases out 67. Hence, the average postoperative change in serum Pg I does not depend on the result of the Hollander test.

The most peculiar finding was the convergence of the Pg I values of DU and GU patients after the operation. The difference between Pg I levels of the DU and GU groups was not significant either 3 months or 1 year after gastric surgery.

Postoperative changes of Pg I depending on the preoperative BAO levels in the DU group. The differences between Pg I in the high, normal and low BAO groups were not significant before the operation (Fig. 2). 3. months after the operation the decrease of Pg I in group A was 29 %, in group B 45 %, and in group C 55 %. A statistically significant difference in absolute values of Pg I concentrations was found only between groups with high (A) and low (C) preoperative BAO ($p < 0.05$).

From 3 months to 1 year after the operation, a statistically reliable decrease of Pg I continued in groups A and B ($p < 0.001$), while in group C the Pg I values remained practically at the same level. One year after the operation the Pg I values differed in groups whose preoperative BAO levels had been high (A) and normal (B) ($p < 0.05$) (Fig. 2).

Changes in Pg I depending on the method of the operation. Serum Pg I concentration decreases after the surgery not depending on the method of the operation (Fig. 3). The decrease after TV + P and TV + AE was not significant within 3 months ($p > 0.05$). During the following 9 months the Pg I values in the TV ± P and TV ± AE groups reached those of the other methods of the operation.

Individual postoperative course of Pg I in the UD group. The individual courses of Pg I after the operation were divergent. The main variants were as follows: decrease (45 cases out of 77) or no changes (21 cases) during the first 3 months, then continuing decrease (36 cases out of 45) or staying on the initial level during the next 9 months was observed. In 9 cases the 3 months' values were even higher than the preoperative ones, in two patients the increase did not stop during the next nine months.

3 months after the operation there were only 10 patients having high Pg I values (Table 1). 11 patients out of 69 had Pg I values below 50 μg/l (16 %), 7 of them below 40 μg/l, 1 year after the operation 20 patients out of 65 examined had the Pg I level below 50 μg/l (31 %), 10 out of them below 40 μg/l (15 %). At the same time the gastric body mucosa had not changed significantly.

Table 1

Level of serum pepsinogen I before and after operation

Level, µg/l	DU			GU		
	Before operation	3 months after operation	1 year after operation	Before operation	3 months after operation	1 year after operation
High > 150	38	10	2	1	1	-
Normal 50-150	44	48	43	10	6	5
Low < 50	-	11	20	-	3	5

Discussion

According to the data of several authors the serum Pg I level reflects the chief cell mass and the actual synthesis of Pg I in the gastric glands /3, 5, 8/. We have seen Pg I in one and the same individual remain stable in the course of several years /6/. The serum Pg I concentration correlates to both basal and pentagastrin-stimulated amounts of pepsin, secreted into the gastric lumen /5/. It seems, however, that the connection between Pg I and BAO is not firm /1, 3, 4, 5/. We observed a little higher Pg I values (1 year after the operation) in these DU patients whose preoperative BAO was high. In all other cases we were not able to demonstrate different responses of Pg I and BAO. The results are in accordance with the fact that Pg I and HCl are produced by different cells, chief and mucous neck cells and parietal cells respectively.

Our finding in the DU and GU groups agree with those of other authors /1, 9/: Pg I in duodenal ulcer is, on average, higher than in controls or GU patients. However, the main part of the Pg I values in DU cases remain within the limits of the norm. Remarkably high Pg I (> 210 µg/l)occurred only in 13 % of cases. In total 46 % of cases were above the limit of the norm. Hence, a non-increased Pg I level seems to be common of DU patients.

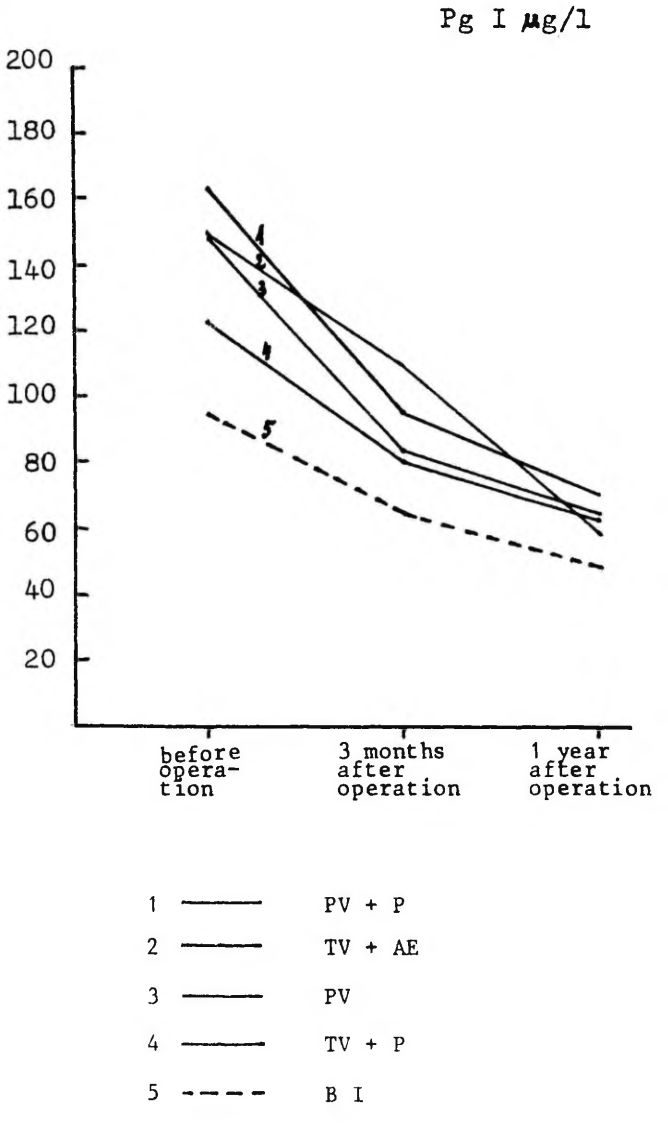


Figure 3. Average decrease of Pg I in DU and GU patients operated by different methods

Selective vagotomy with or without pyloroplasty causes a reduction both in the secretion of pepsin /10, 11/ and serum Pg I /1, 2, 3/ during 1 - 3 postoperative months. Our studies confirm that the decrease of the average Pg I level continues at least up to 1 year, altough the rate of the reduction slows down.

At last two prerequisites seem to be essential for the production of Pg I in normal amounts: sufficient number of chief cells and maintenance of vagal innervation. Partial gastrectomy and different types of vagotomy resulted in a similar reduction of Pg I serum values. At the same time the concentration of Pg I did not decrease as much as for example BAO (Fig. 1). In most cases the synthesis of Pg I remained normal during one year after the operation, still it was at a lower level than before the operation.

At the end of the postoperative year abnormally low Pg I was observed in 31 % of DU patients. At that time no changes detectable by light-microscopy were found in the body mucosa. It is not excluded that some changes in chief cells might be present at the subcellular level, as was recently demonstrated in connection with parietal cells after vagotomy /12/. Scanning the divergent individual courses of Pg I after the operations, it seems probable that the chief cells might respond to the cessation of vagal innervation at least in two ways: reduction of Pg I production (majority of cases) or keeping it on the previous level (minority). A longer follow-up period should clarify whether such behaviour after vagotomy continues more than one year.

REFERENCES

1. Samloff I. M., Secrist D. M., Passaro E. Jr. // Gastroent. - 1976. - Vol. 70. - P. 309-313.
2. Lalla M., Paimela H., Räsänen V. // Scand. J. Gastroent. - 1983. - Vol. 18. - P. 397-399.
3. Äärimaa M., Härkönen M., Varis K., Inberg M., Karonen S.-L. // Scand. J. Gastroent. - 1987. - Vol. 22. - P. 956-960.
4. Samloff I. M., Secrist M. D., Passaro E. Jr. // Gastroent. - 1975. - Vol. 69. - P. 1196-1200.

5. Waldum H. L., Burhol P. G., Straume B. K. // Scand. J. Gastroent. - 1978. - Vol. 13. - P. 943-946.

6. Tamm A., Villako K., Härkönen M., Karonen S.-L // Scand. J. Gastroent. - 1984. - Vol. 9. - P. 1091-1094.

7. Villako K., Tamm A., Savisaar E., Ruttas M. // Scand. J. Gastroent. - 1976. - Vol. 11. - P. 817-822.

8. Samloff I. M. // Gastroenterology. - 1971. - Vol. 61. - P. 185-188.

9. Ichinose M., Miki K., Furihata C., Kageyama T., Hagashi R., Niwa H., Oka H., Matsushima T., Takahashi K. // Clin. Chim. Acta. - 1982. - Vol. 126. - P. 183-191.

10. Clarke R. J., Allan R. N., Alexander-Williams J. // Gut. - 1972. - Vol. 13, N 11. - P. 894-899.

11. Brückner W. L. // Vagotomy / Ed. by F. Holle, S. Andersson. - Berlin, Heidelberg, New York: Springer Verlag, 1974. - P. 87-88.

12. Äärimaa M., Söderström K.-O., Kalimo H., Inberg M., Nevalainen T. // Scand. J. Gastroent. - 1984. - Vol. 19. - P. 787-797.

The Effect of Vagotomy and Antrectomy on Serum Pepsinogens I and II

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Peetsalu A, Tamm A, Härkönen M, Varis K, Sipponen P, Karonen S-L, Väli T, Villako K. The effect of vagotomy and antrectomy on serum pepsinogens I and II. Scand J Gastroenterol 1990, 25, 455–461

Ninety-seven consecutive patients with gastric surgery for peptic ulcer were studied; 86 had duodenal ulcer (DU), and 11 gastric ulcer (GU). DU patients were surgically treated by proximal vagotomy, proximal vagotomy and pyloroplasty, truncal vagotomy and pyloroplasty, or truncal vagotomy and antrectomy. All GU patients were operated on by the Billroth I method. Serum pepsinogen I (S-PG I), serum pepsinogen II (S-PG II), basal acid output (BAO), and maximal acid output (MAO) were determined before and 3 months and 1 year after the operation. The mean preoperative S-PG I concentration in DU patients (154 ± 7 µg/l; mean ± SE) was significantly higher than that (97 ± 9 µg/l) in GU patients ($p < 0.001$). A significant decrease in the mean S-PG I concentration in DU patients was seen 3 months (92 ± 6 µg/l) and 1 year (66 ± 4 µg/l) after the operation ($p < 0.001$). This change did not depend on the type of vagotomy. However, this decrease was not seen in all individual patients as it was in BAO values. Moreover, the mean BAO decrease was much greater at 3 months (7% of the preoperative value) and 1 year (23%) after the operation than the respective decrease in S-PG I concentration. There was also no correlation between S-PG I and acid output (BAO and MAO) before and after the operation. In GU patients the decrease in mean S-PG I value after the Billroth I operation was smaller than in DU patients after vagotomy. Preoperatively, the mean S-PG II did not differ significantly between DU and GU patients. It tended to decrease after the operation in both groups, but the decrease was not statistically significant. Antrectomy had no significant effect on S-PG II level, which indicates that the contribution of the antrum to the total pool of PG II is small. Patients with superficial gastritis in the gastric body mucosa tended to have higher serum pepsinogen levels than patients with normal gastric body mucosa. The mean preoperative serum PG I/PG II ratio was 10.4 ± 0.5 in DU patients and 6.8 ± 1 in GU patients ($p < 0.001$). A significant decrease in the serum PG I/PG II ratio was found in all patient groups 1 year after the operation. The mean preoperative S-PG I – S-PG II difference was 136 ± 7 µg/l in DU patients and 77.8 ± 7 µg/l in GU patients ($p < 0.01$). The S-PG I – S-PG II difference showed the most marked postoperative decrease of all pepsinogen variables measured in this study. This study indicates that the correlation between serum pepsinogen levels and acid secretion variables is poor, and that acid secretion studies are superior in the evaluation of the gastric secretion status before and after different types of gastric surgery in patients with peptic ulcer.

Key words: Duodenal ulcer; gastric mucosa; gastric ulcer; pepsinogens; stomach; vagotomy

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The levels of serum pepsinogen I (S-PG I) and serum pepsinogen II (S-PG II) have been suggested to reflect the functional and morphologic status of the gastric mucosa (1). The concentration of S-PG I is stable at an individual level (2), and it has been shown to correlate with basal and stimulated output of pepsinogens secreted into the gastric lumen (3). Therefore, the serum pepsinogen levels may give information about altered gastric secretion in patients with peptic ulcer disease and about changes in gastric secretion after gastric operations.

An elevated S-PG I is a major risk factor for duodenal ulcer in some patient groups, whereas an elevated S-PG II and a low S-PG I/S-PG II ratio are risk factors for gastric ulcer (4). The purpose of gastric operations in the treatment of peptic ulcer disease is to reduce acid and pepsinogen secretion. The level of S-PG I decreases significantly after a proximal vagotomy for duodenal ulcer (5–8), whereas the level of S-PG II does not change significantly after this type of gastric surgery (7). Nor does a partial gastrectomy have any significant effect on S-PG II level (9), and S-PG II falls significantly after a total gastrectomy (10).

The aim of the present study was to examine the effect of different types of gastric surgery for peptic ulcer disease on the S-PG I and S-PG II levels during a 12-month follow-up period. This information, a kind of 'serum biopsy of the gastric mucosa', has been correlated with the changes in hydrochloric acid secretion and the histology of the gastric mucosa. To obtain all information from the results, we have analyzed not only the data on S-PG I and S-PG II but also the data on the S-PG I/II ratio and S-PG I – S-PG II difference.

SUBJECTS AND METHODS

Subjects

Ninety-seven consecutive patients were studied. All of them had undergone surgery at the Surgical Gastroenterology Dept. of the Tartu University Hospital in 1981–1983 (Table I). The endoscopic diagnosis was confirmed at operation in all cases. In 86 duodenal ulcer (DU) patients 4 methods of surgery were used: proximal vagotomy (PV) (27 cases), proximal vagotomy and pyloroplasty (PV + P) (36 cases), truncal vagotomy and pyloroplasty (TV + P) (16 cases), and truncal vagotomy with antrectomy (TV + AE) (7 cases). The choice of surgical method in the DU patients depended on the level of the gastric secretion and on the pathologic changes in the stomach, pylorus, and duodenum. Table I shows the age and sex distribution in patient groups undergoing different operations.

Table I. The age and sex distribution in patient groups undergoing different operations

Operation*	No. of patients	Age, years (mean ± SD)	Sex, *n*	
			M	F
PV	27	41 ± 11	24	3
PV + P	36	41 ± 11	32	4
TV + P	16	47 ± 11	16	—
TV + AE	7	44 ± 10	6	1
B I	11	47 ± 7	8	3

* PV = proximal vagotomy; PV + P = proximal vagotomy + pyloroplasty; TV + P = truncal vagotomy + pyloroplasty; TV + AE = truncal vagotomy + antrectomy; B I = partial gastrectomy Billroth I.

A comparative study was carried out in 11 gastric ulcer (GU) patients, who underwent classical partial gastrectomy in accordance with the Billroth (BI) method. Thus, the latter was the only group in which vagotomy was not performed.

Serum pepsinogens

PG I and PG II were determined in the blood serum under basal conditions. The sera were stored at −20°C until the determination of PG I (2) and PG II (11) by a radioimmunologic method. The normal range for S-PG I values was considered to be 50–150 μg/l (2), and for S-PG II values it was considered to be 8–35 μg/l (A. Tamm, M. Härkönen, K. Villako et al., unpublished data).

Of 86 DU patients S-PG I was determined 3 times (preoperatively and 3 months and 1 year after the operation) in 57 cases and twice in 25 cases. S-PG II was determined 3 times in 45 and twice in 34 patients. The preoperative serum

Table II. Histologic findings of the gastric body mucosa

	DU patients				GU patients			
	N*	SG	AG	Total	N	SG	AG	Total
Preoperative, *n*	20	21	0	41	0	6	0	6
1 year postop., *n*	9	26	0	35	1	4	0	5

* N = normal; SG = superficial gastritis; AG = atrophic gastritis.

concentrations of PG I and PG II were determined in all but one case.

Gastric acid

Gastric acid was collected from a previously emptied stomach during 60 min by continuous aspiration for the determination of basal acid output (BAO). The maximal acid output (MAO) was determined by collecting gastric juice with continuous suction of two 30-min fractions. The position of the tube in the stomach was checked roentgenologically.

Histology

The histologic findings of the gastric body mucosa were classified in five stages (12). Table II shows the preoperative and postoperative status of the gastric body mucosa in DU and GU patients. None had atrophic gastritis preoperatively or 1 year after the operation.

Statistics

In statistical analysis of the data the Mann–Whitney U-test for unpaired and the Wilcoxon test for paired groups and the chi-square criterion were used.

RESULTS

Serum pepsinogen I

The preoperative serum S-PG I values in DU patients varied between 50 and 405 μg/l, the mean being 154 ± 7 μg/l (±SE). In most of the patients (53%) the values were within the normal range. In 40 cases (47%) the values were above 150 μg/l. In 13 of the latter group (15% of the total) S-PG I exceeded 210 μg/l, which should be considered particularly high. The S-PG I values were normal before the operation in all GU patients except for one patient with a value of 176 μg/l. The mean preoperative S-PG I concentration in the GU patients (97 ± 9 μg/l) was significantly lower than the respective value in DU patients ($p < 0.001$).

The mean of the S-PG I level of the DU patients was significantly lower 3 months and 1 year after the operation than before the operation ($p < 0.001$), the absolute values being 92 ± 6 μg/l and 66 ± 4 μg/l. The respective values for GU patients were 66 ± 1 μg/l and 51 ± 8 μg/l. In the latter group the decrease of the mean S-PG was statistically significant ($p < 0.05$) only 1 year after the operation.

Fig. 1 shows the changes of mean S-PG I after different types of gastric operations. During 1 year after the operation the decrease in the mean S-PG I was statistically significant and of the same order in all treatment groups in DU patients. In GU patients the decrease in mean S-PG I after the BI operation was proportionally smaller, but still significant.

S-PG I could be correlated with the gastric body mucosal histology preoperatively in 41 patients and 1 year later in 35 DU patients. The mean S-PG before the operation was 138.0 ± 12 μg/l in 20 patients with a normal gastric body mucosa and 161.5 ± 13.6 μg/l in 21 patients with superficial gastritis. One year postoperatively the respective mean figures of S-PG I were 62.2 ± 7.9 μg/l and 69.6 ± 7.9 μg/l. The differences were, however, not statistically significant.

Serum pepsinogen II

The preoperative S-PG II concentrations in DU patients varied between 4 and 67 μg/l, the mean value being 17.3 ± 1.2 μg/l. In 89% of them the S-PG II was in the normal range, in 6% high, and in 5% low. In GU patients the mean level of S-PG II was 19.1 ± 5.1 μg/l, which is very similar to that of DU patients.

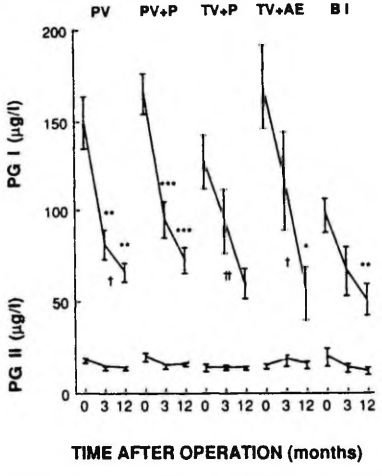

Fig. 1. Serum pepsinogen levels before (0) and after (3 months and 12 months) different operations (PV = proximal vagotomy; PV + P = proximal vagotomy and pyloroplasty; TV + P = truncal vagotomy and pyloroplasty; TV + AE = truncal vagotomy and antrectomy; B I = Billroth I operation). The Wilcoxon test was used for statistical analysis. The bars represent SEs. * $p < 0.05$ compared with the preoperative value; ** $p < 0.01$; *** $p < 0.001$; † $p < 0.05$ between the 3- and 12-month values after the operation; and †† $p < 0.01$.

The changes of mean S-PG II values were not marked in DU patients and in GU patients 3 months and 1 year after different types of operations and were in most cases statistically insignificant (Fig. 1). S-PG II could be correlated with the gastric body mucosal histology preoperatively in 41 patients and 1 year after the operation in 30 DU patients. Patients with superficial gastritis had higher PG II values than others with normal body mucosa, 21.7 ± 3.1 and 15 ± 1.5 µg/l, respectively. After 1 year the corresponding values were 14.4 ± 1.5 and 13.5 ± 0.9 µg/l. The differences were not statistically significant.

In DU patients the concentrations of PG I and PG II correlated with each other preoperatively ($r = 0.536$, $p < 0.01$) and 3 months after the operation ($r = 0.571$, $p < 0.01$). One year after the operation the correlation was not observed ($r = 0.124$, $p > 0.05$).

The ratio and the difference of serum pepsinogen I and pepsinogen II

The mean preoperative serum PG I/PG II ratio was 10.4 ± 0.5 in DU patients and 6.8 ± 1.0 in GU patients, the difference being statistically significant ($p < 0.001$). Fig. 2 shows the changes of serum PG I to serum PG II ratio 3 months and 1 year after the operation in different patient and treatment groups. The decreases in mean values were similar, although not as marked as the decreases in mean serum PG I. A significant decrease in mean serum PG I/PG II ratio was found in all groups of patients 1 year after the operation.

The mean preoperative S-PG I – S-PG II dif-

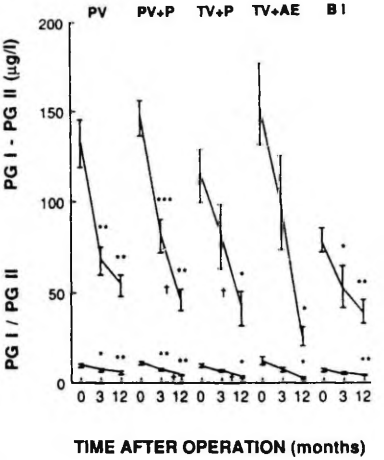

Fig. 2. Serum pepsinogen I/pepsinogen II (PG I/PG II) ratio and difference (PGI – PG II) before and after (3 months and 12 months) different operations (PV = proximal vagotomy; PV + P = proximal vagotomy and pyloroplasty; TV + P = truncal vagotomy and pyloroplasty; TV + AE = truncal vagotomy and antrectomy; B I = Billroth I operation). The Wilcoxon test was used for statistical analysis. The bars represent SEs. * $p < 0.05$ compared with the preoperative value; ** $p < 0.01$; *** $p < 0.001$; and † $p < 0.05$ between the 3- and 12-month values after the operation.

ference was 136 ± 6.8 μg/l in DU patients and 77.8 ± 6.7 μg/l in GU patients, the difference being statistically significant ($p < 0.01$). The postoperative differences were statistically significant 3 months and 1 year later in all treatment groups. It seems that the PG I – PG II difference was the most marked of all postoperative pepsinogen variables measured in this study (Figs. 1 and 2).

Hydrochloric acid output and pepsinogens

The mean preoperative BAO and MAO in DU patients were 6.2 ± 0.7 mmol/h and 24.9 ± 1.5 mmol/h, respectively. The respective preoperative values for GU patients were 1.5 ± 0.4 mmol/h and 8.9 ± 2.2 mmol/h. The BAO was high in 57% of the DU patients preoperatively, within the normal range in 33% and low in 10%.

Three months after the operation the mean BAO value was only 7% of the preoperative one in the PV group, in whom the pyloric function is not affected by the operation, which demonstrates the completeness of the vagotomy. During 4–12 follow-up months BAO increased up to 23%. Corresponding values for MAO were 21% and 29%, respectively (Fig. 3). In the other groups with pyloroplasty, antrectomy, or partial gastrectomy acid output behaved similarly. These results are expected to be less correct because of open passage through the pylorus; therefore no figures are shown.

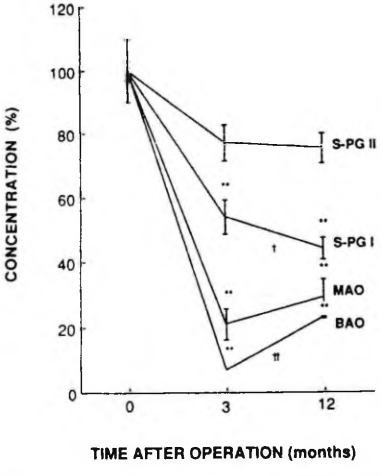

Fig. 3. Mean percentual postoperative changes in serum pepsinogens and gastric acid values in duodenal ulcer (DU) patients after the proximal vagotomy operation. Preoperative values are taken as 100%. The Wilcoxon test was used for statistical analysis. The bars represent SEs. ** $p < 0.01$ compared with the preoperative value; † $p < 0.05$ between the 3- and 12-month values after the operation; and †† $p < 0.01$.

No correlation whatsoever was observed between S-PG I and acid output (BAO and MAO) before and after the operation in DU patients (r values varied between −0.188 and 0.199 and were statistically not significant).

DISCUSSION

The present study was devoted to the examination of the effects of different types of vagotomy and antrectomy on the serum pepsinogen levels. Both proximal and truncal vagotomy had a significant diminishing effect on the serum PG I level but did not affect the serum PG II concentration. Earlier studies have shown a similar decrease in serum PG I in DU patients after proximal vagotomy (5–8), but knowledge about the effect of vagotomy on the serum PG II level is limited (7). These results indicate that vagal tone has a significant effect on the synthesis and/or release of PG I from peptic cells and further on serum PG I level. In contrast, the serum PG II level seems not to be dependent on vagal function but tends to remain unchanged after different types of vagotomy. The serum PG II level may reflect the part of the gastric mucosal secretion which is independent of vagal control.

The present study demonstrates a poor correlation between the serum pepsinogen levels and the hydrochloric acid secretion. Similar findings have been published earlier concerning S-PG I (13). The finding is in accordance with the fact that secretion components are produced by different cell populations and many other independent factors, such as duodenogastric reflux, gastric mucosal oedema, and the metabolic rate of pepsinogens in the blood.

Serum PG I tends to increase during the development of superficial gastritis (14) and decreases during the progress of glandular atrophy. None of our patients had atrophic gastritis during the period of observation. Therefore, the decrease in S-PG I after the operation cannot be explained by this factor. In superficial gastritis the mean S-PG I tends to be higher than in subjects with a normal gastric mucosa, and this was also our finding in the present study. This phenomenon may be caused by mucosal oedema, which may inhibit the flow of pepsinogens into the gastric lumen and, as a consequence, may increase the proportion of pepsinogens delivered into the blood serum. Theoretically, it is possible that a 'stasis' of pepsinogens in the gastric mucosa in the context of inflammatory oedema may have a disadvantageous effect on mucosal resistance in ulcer patients.

Serum PG II did not show similar changes. It has been shown that the S-PG I/S-PG II ratio decreases linearly with the progress of chronic gastritis through different stages of superficial gastritis and atrophic gastritis and gives better information on the morphologic status of the gastric body mucosa than S-PG I alone (1). The present study indicates that the S-PG I/S-PG II ratio is not better than S-PG I alone in the evaluation of functional changes of the gastric body mucosa after surgery.

When a fraction of serum PG I, which is of the same size as serum PG II, is subtracted from total serum PG I, there remains a fraction of serum PG I which could reflect changes in vagal tone more sensitively than total serum PG I. In the present study this leftover fraction (S-PG I − S-PG II) tends to demonstrate more markedly than serum PG I alone the postoperative changes of pepsinogen secretion.

The present study is to our knowledge the first that has enabled the comparison of the effect of different types of vagotomy on S-PG I and PG II levels over a 12-month follow-up period. Proximal vagotomy excludes parasympathetic innervation from the gastric body mucosa, and truncal vagotomy from all parts of the stomach and duodenum. Both operations reduced S-PG I significantly but did not change the S-PG II levels extensively. One can conclude that the reduction of S-PG I observed at the end of the 1st postoperative year did not depend on the type of vagotomy.

The decrease in the S-PG I concentration seems to coincide with the reduction in pepsin secretion (15, 16). The decrease continued at least up to 1 year, although at a decreasing rate. Thus, the severance of the vagal innervation has a long-lasting effect on the cells producing PG I but not on those responsible for PG II secretion.

Reduction of S-PG I values was observed without vagotomy in GU patients after classical partial gastrectomy, which removes the pylorus, antrum, and part of the gastric body. In this group the decrease in S-PG I could have been caused by removal of that part of the gastric body mucosa where the main mass of PG I-producing cells resides.

The decrease in S-PG I after truncal vagotomy with antrectomy is most likely caused by severance of the vagal innervation or by switching off an antral regulatory mechanism. The latter seems not to play an essential role, as the decrease in PG I does not differ in patients who underwent antrectomy or truncal vagotomy with pyloroplasty. Because none of our patients had atrophic changes during the 1-year postoperative follow-up study, glandular atrophy cannot explain the postoperative decrease in S-PG I.

One of the unexpected results of our examination was that antrectomy did not greatly affect the S-PG II level, although pyloric glands belong to the producers of PG II; this is demonstrated by the similarity of the results after TV + P and TV + AE. Our results show that the contribution of the antrum to the total pool of PG II is small or that the residual mass of PG II-producing cells compensates for the fallout pyloric glands. As total gastrectomy causes more than a tenfold decrease in S-PG II, the extragastric (that is, duodenal) sources of serum PG II may be regarded as unessential (10). Hence, the main portion of serum PG II should still originate from cells situated in the proximal regions of the gastric mucosa, like chief cells and mucous neck cells in the fundal or/and cardiac area.

This study confirmed the earlier observation

that proximal gastric vagotomy reduces acid secretion and S-PG I level, but not S-PG II level (7), and showed for the first time that truncal vagotomy had similar effects. Accordingly, the size of S-PG II may reflect the magnitude of pepsinogen secretion not under vagal control. This may explain why the S-PG I – S-PG II difference showed postvagotomy changes most markedly of all pepsinogen variables studied. Antrectomy had no significant effect on S-PG II level, which indicates that a major proportion of this serum pepsinogen group originates from the gastric body mucosa. Accordingly, not only acid secretion but also the level of all serum pepsinogen fraction reflects the morphologic and functional status of this mucosal area. The heterogeneity of peptic cell populations, the production, storing, and release of pepsinogens from the peptic cells, and the metabolism of pepsinogens is obviously more complicated than the secretion of hydrochloric acid from just one separate cell population, parietal cells. This may explain why serum pepsinogen levels and acid secretion variables correlate poorly, why acid secretion studies give more sensitive and specific information about gastric secretion status than serum pepsinogen determinations, and why all attempts to replace acid secretion studies with more convenient serum pepsinogen measurements have failed so far.

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REFERENCES

1. Samloff IM, Varis K, Ihamäki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology: a study in relatives of patients with pernicious anemia. Gastroenterology 1982, 83, 204–209
2. Tamm A, Villako K, Härkönen M, Karonen S-L. Serum pepsinogen I and the state of gastric mucosa in an Estonian population sample. Scand J Gastroenterol 1984, 19, 1091–1094
3. Waldum HL, Burhol PG, Straume BK. Serum group I pepsinogens and gastrin in relation to gastric H^+ and pepsin outputs before and after subcutaneous injection of pentagastrin. Scand J Gastroenterol 1978, 13, 943–946
4. Samloff IM, Stemmermann GN, Heilbrun LK, Nomura A. Elevated serum pepsinogen I and II levels differ as risk factors for duodenal ulcer and gastric ulcer. Gastroenterology 1986, 90, 570–576
5. Haukland HH, Waldum HL, Johnson JA. Effect of proximal gastric vagotomy on insulin-induced gastric H^+ and pepsin secretion and serum group I pepsinogens. Scand J Gastroenterol 1982, 17, 555–559
6. Äärimaa M, Härkönen M, Varis K, Inberg M, Karonen S-L. Serum group I pepsinogens during insulin and pentagastrin tests in unoperated and vagotomized duodenal ulcer patients. Scand J Gastroenterol 1987, 22, 956–960
7. Feldman M, Blair AJ, Richardson CT, Samloff IM. Effect of proximal gastric vagotomy on serum pepsinogen I and II concentrations and acid secretion in duodenal ulcer patients. Dig Dis Sci 1988, 33, 824–827
8. Paimela H, Lalla M, Räsänen V. Serum group I pepsinogens after consecutive stimulations with insulin and pentagastrin in unoperated duodenal ulcer patients and in duodenal ulcer patients after proximal gastric vagotomy. Scand J Gastroenterol 1984, 19, 52–55
9. Sipponen P, Samloff IM, Saukkonen M, Varis K. Serum pepsinogens I and II and gastric mucosal histology after partial gastrectomy. Gut 1985, 26, 1179–1182
10. Ichinose M, Miki K, Furihata C, et al. Radioimmunoassay of group II pepsinogen in human serum. Clin Chim Acta 1982, 122, 61–69
11. Paimela H, Härkönen M, Karonen S-L, Tallgren LG, Stenman S, Ahonen J. Relation between serum group II pepsinogen concentration and the degree of Brunner's gland hyperplasia in patients with chronic renal failure. Gut 1985, 26, 198–202
12. Villako K, Tamm A, Savisaar E, Ruttas M. Prevalence of antral and fundic gastritis in a randomly selected group of an Estonian rural population. Scand J Gastroenterol 1976, 11, 817–822
13. Goedhard JG, Biemond I, Giliams JP, Pals G, Kreuning J. Serum pepsinogen I levels: assessment of gastric acid secretion? In: Kreuning J, Samloff IM, Rotter JI, Eriksson AW, eds. Pepsinogens in man: clinical and genetic advances. Alan R. Liss, New York, 1985 (Prog Clin Biol Res; 173), 139–146
14. Varis K, Salmi HA, Cederberg A, Sarna S, Härkönen M. Pepsinogens in peptic ulcer disease and in non-ulcer dyspepsia. Hepatogastroenterology 1989, 36, 45
15. Clarke RJ, Allan RN, Alexander-Williams J. The effect of retaining antral innervation on the reductions of gastric acid and pepsin secretion after vagotomy. Gut 1972, 13, 894–899
16. Brückner WL. In: Holle F, Andersson S, eds. Vagotomy. Springer Verlag, Berlin, 1974, 87–88

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Long-Term Effect of Vagotomy on Gastric Mucosa and *Helicobacter pylori* in Duodenal Ulcer Patients

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Peetsalu A, Maaroos H-I, Sipponen P. Peetsalu M. Long term effect of vagotomy on gastric mucosa and *Helicobacter pylori* in duodenal ulcer patients. Scand J Gastroenterol 1991. 26(suppl 186), 77-83

The purpose of the study was to evaluate the long-term effects of vagotomy on the morphological status and *Helicobacter pylori* infestation of the gastric mucosa. Endoscopy with biopsies (2 from antrum and 2 from corpus) was performed in 317 patients on whom vagotomy had been performed on an average 8 years earlier. The success of the vagotomy was estimated by the endoscopic Congo Red technique in 270 cases. Non-operated 187 duodenal ulcer patients were examined endoscopically and bioptically in a similar way and used as a reference series. *Helicobacter pylori* (HP) was determined by Giemsa staining of biopsy specimens in both series. In non operated duodenal ulcer patients, gastritis and HP behaved as expected from the data in literature: antral gastritis was present in nearly all cases (96%), while the corpus mucosa was normal or the process was retarded at the stage of superficial gastritis (76%) and atrophic changes were virtually lacking (1%). On the basis of the Congo Red test the vagotomized patients were separated into two groups: successfully operated, *i.e.*, complete vagotomy, and incomplete vagotomy groups. The results of the examinations were independent of the kind of vagotomy performed, but related significantly to its completeness. The incomplete and complete groups differed significantly. The prevalence of atrophic changes (29%) in the corpus was significantly higher and that of superficial gastritis (69%) lower in the complete than in the incomplete vagotomy group, in which the prevalences were 12% and 85%, respectively. Likewise the prevalence and density of HP was lower in the complete vagotomy group but the difference was not statistically significant. The antral mucosa did not significantly differ morphologically in the two groups, but the overall prevalences of HP and of high density colonization of the bacterium was significantly lower in the complete group. Summarizing, the effects of vagotomy were dependent upon the success rather than the type of vagotomy, and the most significant long-term effects of successful vagotomy were the appearance and progression of atrophic changes in the corpus and the overall decrease of HP positivity as compared with patients with incomplete vagotomy.

Key words: Vagotomy; follow-up; gastritis; *Helicobacter pylori*

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Chronic antral gastritis and *Helicobacter pylori* infestation are present in most cases of active duodenal ulcer. It also has been shown that eradication of the bacteria may reduce the recurrence rate of the disease. On the other hand, very little is known of the long-term effects of the most commonly used operative procedure, the vagotomy, on the morphological state and *Helicobacter pylori* infestation of the gastric mucosa. For this reason we have studied by morphological and bacterioscopical examinations a large series of duodenal ulcer patients on an average 8 years after vagotomy. The main effect of vagotomy is a decrease in gastric acid output, which therefore can be used for estimation of the effectivity of the operative

procedure. In the present study we estimated the completeness of vagotomy by the Congo Red technique and were for this reason able to compare the completeness of vagotomy with the antral and corpus mucosal morphology and the *Helicobacter pylori* findings. In addition, a large series of non-operated duodenal ulcer patients have been examined in a similar way by morphological methods and Giemsa staining for use as reference material.

MATERIAL AND METHODS

Consecutive 317 vagotomized duodenal ulcer (DU) patients were studied. All of them had undergone vagotomy at the Second Department of Surgery, Tartu University Hospital, Tartu, Estonia, in 1976-1984 (Table I): 230 patients had undergone proximal vagotomy (PV) and, in addition to PV, drainage procedures had been performed in 147 of these 230 cases (127 pyloroplasty and 20 gastroduodenostomy Jaboulay); 87 patients had undergone truncal vagotomy with drainage (77 pyloroplasty and 10 gastroduodenostomy Jaboulay). Table I shows the age and sex of the patients and the follow-up time after different types of vagotomy. The patients were contacted and interviewed as outpatients, a symptom questionnaire was filled out and each patient was offered endoscopy.

Two biopsy specimens were taken from the antral mucosa and two from the body mucosa after checking up the oesophagus, stomach and duodenum. From 281 of the 317 operated patients specimens were obtained from both antrum and corpus mucosa and from the remaining 36 from either antrum or corpus. The completeness of vagotomy was estimated by the Congo Red test according to Donahue *et al.* (1) in 270 of the 317 cases. Recurrent ulcer was found in 19 (6%) of the cases; vagotomy was incomplete in 18 and complete in one case (NSAID user).

The group of non-operated patients consisted of consecutive 187 symptomatic medically treated DU patients who were endoscopically examined at the Gastroenterological Department, Tartu University Hospital, Tartu, Estonia. Ulcer history varied from 1 to 20 years, mean 3.5±4.0 (SD) years; mean age was 43±13 (SD) years (127 men, 60 women). None of the patients had received antibiotics before the endoscopy. Two biopsy specimens were taken from both the antral and the corpus mucosa.

Biopsy specimens were fixed overnight in neutral buffered formalin and were embedded in paraffin. Tissue sections were stained for morphological and *Helicobacter pylori* examination by the haematoxylin-eosin and modified Giemsa methods.

The histology of and HP colonisation in the antral and gastric corpus mucosa were classified analogically as described earlier (2): histology: normal, superficial gastritis (slight, moderate, severe) and atrophic gastritis (slight, moderate, severe); HP colonisation: absence of microbes (grade 0); small amounts (grade 1) = less than 20 microbes per field; moderate amounts (grade 2) = 20-60 microbes per field; and large amounts (grade 3) = more than 60 microbes per field.

Statistical methods

Category data were analysed by the χ^2 (chi-square) test, numerical data were analysed by Student's *t*-test; *p*-values below 0.05 were considered significant.

RESULTS

1. Morphology of the gastric mucosa

Marked differences in the behaviour of the corpus mucosa were found between the operated and non-operated patients with duodenal ulcer (Table II). The prevalences of atrophic corpus gastritis in the two groups were 21% and 1%, of superficial gastritis 76% and 76%, and of normal corpus mucosa 3% and 23%, respectively. The differences were statistically significant with regard to any status of the corpus mucosa.

In the antral mucosa (Table II), gastritis was present in both operated and non-operated patients in almost all cases, the prevalences being 99% and 100%, respectively. There were no differences in the degree of antral gastritis

in the two groups.

Table I. Distribution of age, sex, and mean follow-up time since vagotomy in the follow-up groups

Group	No. of patients	Age, years (Mean±SD)	No. of males	No. of females	Follow-up times since vagotomy (Mean±SD)
Proximal vagotomy	230	49±11	198	32	8.2±2.1
Truncal vagotomy	87	50±13	79	8	7.8±2.3
Total study group	317	49±12	277	40	8.1±2.1

Table II. Histological state of the gastric mucosa: A = operated and non-operated groups, B = proximal and truncal vagotomy groups

	State of antral mucosa				State of corpus mucosa			
Group	N* No. (%)	SG No. (%)	AG No. (%)	Total No.	N No. (%)	SG No. (%)	AG No. (%)	Total No.
A								
Non-operated	-	180 (96)	7 (4)	187	42 (23)	143 (76)	2 (1)	187
Operated	3 (1)	275 (92)	20 (7)	298	9 (3)†	228 (76)	63 (21)†	300
B								
Proximal vagotomy	3 (1)	198 (92)	14 (7)	213	6 (3)	169 (77)	43 (20)	218
Truncal vagotomy	-	77 (93)	6 (7)	83	3 (4)	59 (72)	20 (24)	82

*N = normal; SG = superficial gastritis; AG = atrophic gastritis; †$p<0.001$ differences between operated and non-operated groups

Table III. Histological state of the gastric mucosa in the complete and incomplete vagotomy groups

	State of antral mucosa				State of corpus mucosa			
Group	N* No. (%)	SG No. (%)	AG No. (%)	Total No.	N No. (%)	SG No. (%)	AG No. (%)	Total No.
Complete vagotomy	3 (2)	111 (91)	8 (7)	122	3 (2)	89 (69)†	37 (29)†	129
Incomplete vagotomy	-	121 (92)	10 (8)	131	4 (3)	110 (85)	16 (12)	130

*N = normal; SG = superficial gastritis, AG = atrophic gastritis; †$p<0.01$ differences between complete vagotomy and incomplete vagotomy groups

Atrophic gastritis detected after vagotomy was of a moderate degree in 16 cases and of severe degree in 2 cases, while advanced degrees of atrophy were lacking in non-operated patients.

The status of the corpus mucosa in the operated cases did not depend upon the type of vagotomy but rather on its completeness (Tables II and III). Thus the prevalence of atrophic corpus gastritis was significantly ($p<0.01$) higher in the complete vagotomy group (Table III) than in the incomplete, and highly significantly ($p<0.001$) higher than in the non-operated groups. On the other hand, superficial corpus gastritis was significantly lower in the complete than in the incomplete vagotomy group. However, the total prevalence of gastritis in both antrum and corpus was similar in both groups. In the antral mucosa there were virtually no differences between the groups in any respects.

Table IV. HP colonisation in gastric biopsies: A = operated and non-operated groups, B = proximal and truncal vagotomy groups, C = complete and incomplete vagotomy groups

Group	Antrum HP intensity grade					Corpus HP intensity grade				
	0* No. (%)	1 No. (%)	2 (No. (%)	3 No. (%)	Total No.	0 No. (%)	1 No. (%)	2 No. (%)	3 No. (%)	Total No.
A										
Operated	48 (16)†	44 (15)†	35 (11)†	176 (58)‡	303	40 (13)‡	86 (29)‡	41 (14)	133 (44)‡	300
Non-operated	13 (7)	47 (25)	54 (29)	73 (39)	187	54 (29)	89 (47)	20 (11)	24 (13)	187
B										
Proximal vagotomy	33 (15)	30 (14)	26 (12)	130 (59)	219	30 (14)	57 (26)	31 (14)	100 (46)	218
Truncal vagotomy	15 (18)	14 (17)	9 (10)	46 (55)	84	10 (12)	29 (36)	10 (12)	33 (40)	82
C										
Complete vagotomy	32 (25)§	19 (15)	20 (15)	59 (45)§	130	20 (15)	42 (32)	16 (13)	52 (40)	130
Incomplete vagotomy	8 (6)	20 (15)	10 (8)	93 (71)	131	12 (9)	33 (26)	16 (13)	67 (52)	128

*HP intensity grade: 0 = absence of HP; 1 = low HP; 2 = moderate HP; 3 = large HP (for limits between subgroups of HP see Material and Methods)
†$p<0.01$ and ‡$p<0.001$ differences between operated and non-operated groups
§$p<0.001$ differences between complete and incomplete vagotomy groups

Table V. Distribution of HP colonisation according to the histological state of the gastric mucosa in operated and non-operated groups

State of the mucosa	Operated										Non-operated									
	Antrum HP intensity grade					Corpus HP intensity grade					Antrum HP intensity grade					Corpus HP intensity grade				
	0*	1	2	3	Total No.	0	1	2	3	Total No.	0	1	2	3	Total No.	0	1	2	3	Total No.
Normal	3	0	0	0	3	3	4	1	1	9	0	0	0	0	0	22	14	4	2	42
Superficial gastritis	36	36	29	163	264	22	70	18	103	213	13	44	50	73	180	31	74	16	22	143
Atrophic gastritis	7	4	2	7	20	14	11	10	23	58	0	3	4	0	7	1	1	0	0	2
Total	46	40	31	170	287	39	85	29	127	280	13	47	54	73	187	54	89	20	24	187

*HP intensity grade: 0 = absence of HP; 1 = small HP; 2 = moderate HP; 3 = large HP (for limits between subgroups of HP intensity see Material and Methods)

2. Occurrence and density of Helicobacter pylori *infestation*

In similarity to the morphological results, the bacteriology of antral and corpus mucosa appeared rather independent of the type of operation performed (Table IV). However, there were differences in the prevalence and density of HP infestation according to the success of the vagotomy. Thus, in the complete vagotomy group the prevalences of HP infestation in both antral and corpus mucosa were significantly lower (Table IV) than in the incomplete vagotomy group. The same observation was made in regard to high density of bacteria.

When comparisons were made between the complete vagotomy group and the non-operated group it appeared that the prevalence of the HP infestation was in antrum and corpus significantly ($p<0.01$) lower in the complete vagotomy group than in the non-operated cases. On the other hand, the prevalence of subjects with high grade of HP colonisation was in the corpus mucosa significantly ($p<0.001$) higher in the complete vagotomy than in the non-operated group; while no difference was found in this respect with regard to antral mucosa.

3. Helicobacter pylori *and morphology of the gastric mucosa*

As seen from Table V, the HP infestation was mainly associated with signs of superficial inflammation. In superficial gastritis of the antrum, bacteria were present in operated and non-operated cases in 86% and 93%, respectively. In corpus mucosa these percentages were 90% and 78%, respectively.

HP was absent in all cases of morphologically normal antral mucosa. In the normal corpus mucosa of operated patients they were absent in 33% and of non-operated patients in 52% of cases.

DISCUSSION

In the present study we have tried to evaluate the long-term effects of vagotomy on the morphology and HP infestation of the antral and corpus mucosa, with special emphasis on the success of vagotomy in duodenal ulcer patients. Thus the completeness of the vagotomy was examined and a comparison of cases of complete vagotomy with those of incomplete vagotomy is an essential part of the present study.

Comparisons of the complete vagotomy group with the non-operated were handicapped by a number of possible sources of error. The non-operated group represents a group of patients selected by principles different from those of the operated: the age and sex distribution and follow-up times are different. This makes it necessary to consider results of comparisons with the nonoperated cases with some reservation. On the other hand, the series was collected from the same institute, represents the same geographical area and was examined by the authors in the way similar to that used for the operated cases. In addition, the behaviour of gastritis in the non-operated cases was similar to that found in the other studies showing an expected progression of antral and a retardation of corpus gastritis (3,4,5). It should be also noted that the prevalence of atrophic changes in the non-operated group was close to zero, suggesting that the difference from the operated cases would have remained significant even after age- and sex-matching. It was, in fact, found that the prevalences of atrophic changes in the corpus were 21% in the operated but 1% in the non-operated, and the prevalence of normal corpus mucosa was in the two groups 3% and 23%, respectively. Likewise, the prevalence of HP infestation in the corpus was significantly lower in the operated group.

The comparisons performed with different groups showed that the results of the morphological and bacteriological studies were dependent upon the success of the vagotony rather than upon the type of operation used. Thus the complete vagotomy group revealed a significant progression of gastritis in the corpus and a significantly higher prevalence of atrophic changes than in the incomplete vagotomy group. On the other hand, the morphology of

the antral mucosa was on the whole similar in the different groups. The reasons for the dissimilar responses of antral and corpus mucosae are not obvious, but might be due to difference in the immunoresponse of antral and corpus mucosae to bacterial antigens (6,7).

The development and progression of post-vagotomy corpus gastritis has also been noted by some authors (8-13) during shorter follow-up times, however, the changes found were usually less pronounced than those observed in the present study. Some authors (14-18) found no essential difference between operated and non-operated patients.

The reasons for the development of atrophic changes after successful vagotomy are not clear. Elimination of the trophic effect of the vagal drive has been suggested, and some authors (10,11) have found a decrease in size and number of parietal cells shortly after parietal cell vagotomy. Äärimaa *et al.* (13) noted also an increase of round cell infiltration in association with decrease in the number of parietal cells. Similar results have been reported by Jönsson *et al.* (19) who observed the development of atrophic changes in the corpus mucosa 2-3 years after parietal cell vagotomy. An additional explanation might be offered by behaviour of the HP infection. This was present in the antrum of almost all and the corpus of the majority of the non-operated duodenal ulcer patients; atrophic changes were virtually absent, however. In addition, the appearance of atrophic corpus changes after operation were in the present study not accompanied by any consistent changes in the behaviour of HP infestation. Accordingly, the development of atrophic changes can hardly be related to HP infestation. This view is further emphasized by follow-up studies, which suggest that HP infestation is mainly related to the early phases of the gastritic process and that its significance decreases in the atrophic phase of chronic gastritis (2,20). In addition, in the present operated group the prevalence of HP positivity was significantly lower in cases of corpus atrophy than in those without corpus atrophy.

The reduced HP positivity after operation is probably related to the profound changes in the function of corpus mucosa induced by vagotomy. An association with the operation is suggested by the difference in the HP positivity between the complete and incomplete vagotomy groups.

Complete vagotomy lowers the effects of the acid-peptic factor (21), may interfere with prostaglandin synthesis (21), change the composition of mucus, and lead to motor disturbances and other alterations that might create an unfavourable conditions for the survival of the bacteria. It is true that cases of high HP density were significantly more common in the operated than in the non-operated patients, however, the limitations of the non-operated group as a direct control material for the operated group was pointed out above. Moreover, the prevalence of high density HP colonisation was, in fact, somewhat lower in the corpus of complete vagotomy cases than in cases of incomplete operation. It is obvious that solution of morphological and bacteriological problems necessitate a long-term follow-up of cases that originally were adequately studied for this purpose.

REFERENCES

1. Donahue PE, Maroske D, Roeher DH, Nyhus LM. Experience with the endoscopic test for completeness of vagotomy. Results of application in two medical centers. Zenbl Chir 1987, 112, 1208-1215
2. Maaroos H-I, Kekki M, Villako K, Sipponen P, Tamm A, Sadeniemi L. The occurrence and extent of *Helicobacter pylori* colonization and antral and body gastritis profiles in an Estonian population sample. Scand J Gastroenterol 1990, 25, 1010-1017
3. Cheli K, Giacosa A. Duodenal ulcer and chronic gastritis. Endoscopy 1986, 18, 125-126
4. Kekki M, Saukkonen M, Sipponen P, Varis K, Siurala M. Dynamics of chronic gastritis in the remnant after partial gastrectomy for duodenal ulcer. Scand J Gastroenterol 1980, 15, 509-512
5. Kekki M, Sipponen P, Siurala M. Progression of antral and body gastritis in patients with active and healed duodenal ulcer and duodenitis. Scand J Gastroenterol 1984, 19, 382-388
6. Valnes K, Brandtzeg P, Elgjo K, Stave K. Specific and non specific humoral defence factors in the epithelium of normal and inflammed gastric mucosa. Gastroenterology 1984, 86, 402-412
7. Wyatt JI, Rathbone BJ, Dixon MF, Heatley RV.

Local immune response to gastric campylobacter in non-ulcer dyspepsia. J Clin Pathol 1986, 39, 863-879

8. Aase S, Roland M, Liavåg I, Dahl E. Stereological analysis of human parietal cells before and 6 months after vagotomy. Scand J Gastroenterol 1985, 20, 257-267
9. Holle GE. Longzeituntersuchungen der Pundusschleimhaut beim Gastroduodenal Ulkus nach SpV und Pyloroplastik. Z Gastroenterol 1978, 16, 57-65
10. Liavag L, Vaage S. The effect of vagotomy and pyloroplasty on the gastrointestinal mucosa of the rat. Scand J Gastroenterol 1972, 7, 23-27
11. Roland M, Berstad A, Liavag J. Histological study of gastric mucosa before and after proximal gastric vagotomy in duodenal ulcer patients. Scand J Gastroenterol 1975, 10, 181-186
12. Watt PCH, Sloan JM, Kennedy TL. Changes in gastric mucosa after vagotomy and gastrojejunostomy for duodenal ulcer. Br Med J 1983, 287, 1407-1410
13. Ärärimaa M, Söderström K-O, Kalimo H, Inberg M, Nevalainen T. Morphology and function of the parietal cells after proximal selective vagotomy in duodenal ulcer patients. Scand J Gastroenterol 1984, 19, 787-797
14. Dewar EP, Dixon MF, Johnston D. Bile reflux and degree of gastritis after highly selective vagotomy, truncal vagotomy and partial gastrectomy for duodenal ulcer. Wrld J Surg 1983, 7, 743-750
15. Gutierrez O, Lehy T, René E, Grés L, Bonfils S. Epithelial cell proliferation in human fundic and antral mucosae. Influence of superselective vagotomy and relationship with gastritis. Dig Dis Sci 1985, 30, 1034-1042
16. Hirshowitz BI, Helman CA. Effects of fundic vagotomy and cholinergic replacement on pentagastrin dose responsive gastric acid and pepsin secretion in man. Gut 1982, 23, 675-682
17. Lygidakis NJ. Histologic changes after elective surgery for duodenal ulcer. Acta Chir Scand 1986, 152, 139-144
18. Mitsche H. Morphologische Veränderungen der Magenschleimhaut nach vagotomy. Z Gastroenterologie 1979, 17, 493-502
19. Jönsson K-Å, Ström M, Bodemar G, Norrby K. Histologic changes in the gastroduodenal mucosa after long-term medical treatment with cimetidine or parietal cell vagotomy in patients with juxtapyloric ulcer disease. Scand J Gastroenterol 1988, 23, 433-441
20. Siurala M, Sipponen P, Kekki M. *Campylobacter pylori* in sample of Finnish population: relation to morphology and functions of the gastric mucosa. Gut 1988, 29, 909-915
21. Barth H. Hypothesen zur Bedeutung des Histamins und Prostaglandins in der Ulcus Pathogenese. In: Nichtresezierende Ulkuschirurgie. Springer-Verlag, Berlin, Heidelberg, New York, 1980, 9-19

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Operatsioonijärgne endoskoopiline kongo punase test vagotoomia täielikkuse hindamisel

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duodenaalhaavand, vagotoomia, vagotoomia täielikkus, retsidiivhaavand

Duodenaalhaavandi ravimisel pärast vagotoomiat on peamine probleem retsidiivhaavandi tekkimine, mille esinemissagedus aja möödudes pärast operatsiooni suureneb (13). Retsidiivhaavandi tekke üheks peamiseks põhjuseks peetakse mittetäielikku vagotoomiat (11). Tänini ei ole leitud niisugust maohappe sekretsiooni määramise testi, kaasa arvatud laialt kasutatav Hollanderi test, mis lubaks kindlalt prognoosida operatsioonijärgset haavandi retsidiveerumist (10, 14). Meie oleme vagotoomia täielikkuse määramiseks kasutanud suhteliselt vähe levinud endoskoopilist kongo punase testi (EKPT).

Käesoleva töö eesmärgid olid: 1) EKPT alusel hinnata ja võrrelda vagotoomia täielikkust pärast proksimaalset vagotoomiat ja trunkaalset vagotoomiat; 2) määrata mittetäieliku vagotoomia alade lokalisatsioon ja suurus maokorpuse limaskestal ja uurida nende tähtsust retsidiivhaavandi tekkes; 3) võrrelda retsidiivhaavandiga haigetel EKPT tulemusi muude vagotoomia täielikkust hindavate kvantitatiivsete testide, nagu insuliintesti ja öise 12-tunnise maohappesuse reduktsiooni testi tulemustega.

Uurimismaterjal ja -metoodika. Kõigile uuritule tehti EKPT Donahue ja kaasautorite (6) järgi basaaltingimustes, s.t. maosekretsiooni stimuleerimata. Pärast söögitoru, mao ja kaksteistsõrmiku endoskoopilist kontrolli tühjendati magu aspiratsiooni teel. Läbi endoskoobikanali viidi maku peen polüvinüülsond, mille kaudu kaeti silma kontrolli all kogu makorpuse limaskest 0,5%-lise kongo punase lahusega (valmistatud 5,0%-lises naatriumbikarbonaadis). Seejärel aspireeriti liigne värvilahus maost ja 2...3 minuti jooksul jälgiti punase värvuse muutumist mao limaskestal. Alasid, kus maokorpuse limaskesta pinnal oli pH<3,0 ja punane värvus muutus sinakasmustaks, peeti EKPT-positiivseks (viitab mittetäielikule vagotoomiale). Alasid, kus punane värvus ei muutunud (pH>3,0), peeti EKPT-negatiivseks (viitab täielikule vagotoomiale). Vaatluse teel hinnati maokorpuse limaskestal EKPT-positiivsete alade lokalisatsiooni ja suurust. Suureks (hinnang on subjektiivne) arvati EKPT-positiivsed alad, mis moodustasid 20% või rohkem maokorpuse pindalast.

13 juhul võrdlesime retsidiivhaavandiga haigete EKPT tulemusi insuliintesti tulemustega kolme kriteeriumi alusel (1, 3, 16) ja 11 juhul öise 12-tunnise maohappesuse reduktsiooni testi tulemustega (7).

5...12 aastat pärast operatsiooni uuriti 271 patsienti, kellele duodenaalhaavandi tõttu oli aastatel 1977...1984 tehtud vagotoomia ilma selle operatsiooniaegse täielikkuse kontrollita. Mehi oli 236 ja naisi 35, haigete vanus oli uurimise ajal 27 kuni 81 aastat (keskmine vanus 50 aastat). 197 patsienti uuriti keskmiselt 8 aastat pärast proksimaalset vagotoomiat (PV ehk täpsemalt proksimaalne selektiivne vagotoomia). Lisaks PV-le oli selles rühmas 149 patsiendile tehtud kas püloroplastika, duodenoplastika või gastroduodenostoomia Jaboulay järgi, vastavalt 107, 23 ja 19 juhul.

74 patsienti uuriti keskmiselt 8 aastat pärast mõlemapoolset subdiafragmaalset trunkaalset vagotoomiat (TV) koos püloroplastikaga (68 juhul) või gastroduodenostoomiaga Jaboulay järgi (6 juhul). Uurimismaterjali töödeldi statistiliselt Studenti t-testi järgi.

Uurimistulemused ja arutelu. Keskmiselt 8 aastat pärast operatsiooni selgitati EKPT alusel välja mittetäielik vagotoomia pooltel juhtudel, kusjuures oluliselt sagedamini pärast PV-d võrreldes TV-ga, vastavalt 56% (110/197) ja 34% (25/74) (P<0,001) (vt. tabel 1). Seejuures püloroplastika kasutamine lisaks PV-le ei mõjutanud vagotoomia täielikkust: EKPT-positiivseid leidsime pärast PV-d 54%-l (26/48) ja pärast PV-d koos püloroplastikaga samuti 54%-l (54/100) juhtudest (P>0,05). Mittetäieliku vagotoomia alad lokaliseerusid peamiselt maokorpuse ülaosas: pärast PV-d 82%-l ja pärast TV-d 92%-l juhtudest (vahe statistiliselt ebaoluline, P>0,05), võrreldes korpuse allosaga vastavalt 33%-l ja 32%-l juhtudest (P<0,001). Oluliselt vähem oli korpuse allosas mittetäieliku vagotoomia alasid isoleeritult (ilma korpuse ülaosa kaasa haaramata): pärast PV-d 18%-l (20/

110) ja pärast TV-d 8%-l (2/25) juhtudest.

Tabelist 1 selgub, et suuri, maokorpuse pindalast 20% ja ulatuslikumaid mittetäieliku vagotoomia alasid leidsime pärast PV-d 22%-l (24/110) ja pärast TV-d 40%-l (10/25) juhtudest (erinevus oli statistiliselt ebaoluline, P> >0,05). Kõik suured alad lokaliseerusid maokorpuse ülaosas, ulatudes osal juhtudel ka korpuse allossa. Isoleeritult maokorpuse allosas leidsime ainult väikesi, läbimõõduga mõnest millimeetrist kuni 3 cm-ni mittetäieliku vagotoomia alasid.

Retsidiivhaavandeid tekkis 271 uuritust 19-l (7%): 18 juhul oli EKPT järgi vagotoomia mittetäielik ja ühel juhul täielik. Viimane uuritu oli krooniline ultserogeensete medikamentide tarvitaja, kellel maohappe väärtused olid madalad.

EKPT-positiivsete alade olemasolu korral ei sõltunud retsidiivhaavandi teke oluliselt vagotoomia tüübist: pärast PV-d ja TV-d vastavalt 12%-l (13/110) ja 20%-l (5/25) juhtudest (P>0,05). Küll aga tekkis retsidiive tunduvalt sagedamini suurte mittetäieliku vagotoomia alade korral, pärast PV-d 33%-l (8/24) ja pärast TV-d 40%-l (4/10) juhtudest, võrreldes väikeste aladega vastavalt 6%-l (5/86) pärast PV-d (P<0,01) ja 7%-l (1/15) pärast TV-d (P<0,05). Kahel retsidiivhaavandiga patsiendil leidsime pärast PV-d ainult väikesi mittetäieliku vagotoomiaga alasid suure maokõveriku pool korpuse allosas, mida pärast TV-d ei täheldanud. Retsidiivhaavandiga haigete uurimine näitas (vt. tabel 2), et vagotoomia täielikkuse hindamisel andis insuliintest 15%-l (2/13) ja öise 12-tunnise maohappesuse reduktsiooni test 45%-l (5/11) juhtudest EKPT-st erinevaid tulemusi.

Kongo punase test põhineb maohappe spontaanse sekretsiooni-intensiivsuse määramisel basaaltingimustes, mis sõltub uitnärvi talituslikust aktiivsusest (9). EKPT tulemused mittetäieliku vagotoomia juhtudel on kordusuuringutel reprodutseeritavad, mis näitab testi stabiilsust (15). Vahetult pärast operatsiooni on EKPT-ga leitud 11%-l juhtudest mittetäielikku vagotoomiat (15). Meie leidsime sama meetodit kasutades, et keskmiselt 8 aastat pärast operatsiooni on mittetäieliku vagotoomia sagedus pooltel juhtudel suurenenud. Analoogset operatsioonijärgset mittetäieliku vagotoomia sageduse suurenemist on kirjeldatud Hollanderi positiivse testi alusel nii pärast

Tabel 1. Endoskoopilise kongo punase testi positiivsete alade lokalisatsioon ja suurus maokorpuse limaskestal

EKPT-positiivsed alad maokorpuse limaskestal		Proksimaalne vagotoomia		Trunkaalne vagotoomia	
lokalisatsioon	suurus	n (%)	retsidiivhaavandid	n (%)	retsidiivhaavandid
Ülaosa	suur*	22 (20%)	8	7 (28%)	3
	väike**	52 (47%)	3	10 (40%)	1
Allosa	suur	—	—	—	—
	väike	20 (18%)	2	2 (8%)	—
Ülaosa ja allosa	suur	2 (2%)	—	3 (12%)	1
	väike	14 (13%)	—	3 (12%)	—
Kokku		110 (100%)	13	25 (100%)	5

* Üle 20% maokorpuse pindalast (subjektiivne hinnang)
** Üks või mitu ala läbimõõduga mõnest mm-st kuni 3 cm-ni

Tabel 2. Retsidiivhaavandiga haigete jaotumus sõltuvalt vagotoomia täielikkusest

Vagotoomia täielikkuse hindamise test	Vagotoomia täielikkus	
	täielik	mittetäielik
EKPT	—	18
Insuliintest kolme kriteeriumi alusel	2	11
Öine 12-tunnine maohappesuse reduktsiooni test	5	6

proksimaalset vagotoomiat (12) kui ka pärast trunkaalset vagotoomiat (8). Meie andmed näitavad, et pärast proksimaalset vagotoomiat esineb mittetäielikku vagotoomiat oluliselt sagedamini kui pärast trunkaalset vagotoomiat, vastavalt 56%-l ja 34%-l juhtudest, mida varem EKPT alusel ei ole leitud (15). Seejuures püloroplastika kasutamine lisaks proksimaalsele vagotoomiale ei mõju vagotoomia täielikkusele. On oluline, et EKPT võimaldab määrata igal haigel mittetäieliku vagotoomia ala(de) lokalisatsiooni ja suuruse, see on tähtis retsidiivhaavandi tekke prognoosimisel. Andmed näitavad, et sõltumata vagotoomia tüübist, on mittetäieliku vagotoomia alad lokaliseerunud valdavalt (82%-l ja enamalgi juhtudest) maokorpuse ülaosas ja 1/3-l juhtudest allosas. Suured mittetäieliku vagotoomia alad maokorpuse limaskestal lokaliseeruvad samuti valdavalt maokorpuse ülaosas. Meie tulemused näitavad, et peaaegu kõik (18/19) retsidiivhaavandid on seotud maokorpuse säilinud vaagusinnervatsiooniga, seejuures aga kõigist mittetäieliku vagotoomia juhtudest moodustavad retsidiivhaavanditega haiged vaid 13% (18/135) EKPT alusel. Sarnaseid tulesi on kirjeldatud ka varem Hollanderi testi alusel (4). Retsidiivhaavandi teke säilinud vaagusinnervatsiooni alade olemasolul ei sõltu niivõrd vagotoomia tüübist, kuivõrd nende alade suurusest maokorpuse limaskestal. Retsidiivhaavandeid leidsime sagedamini suurte ja põhiliselt maokorpuse ülaosa limaskesta hõlmavate mittetäieliku vagotoomia alade korral: pärast proksimaalset vagotoomiat 33%-l ja pärast trunkaalset vagotoomiat 40%-l juhtudest. Analoogilised andmed retsidiivhaavandite tekke kohta suurte mittetäieliku vagotoomiaga alade olemasolul esitab R. P. Saik (15). Väikeste mittetäieliku vagotoomia alade korral tekib retsidiivhaavandeid harvem, 6. . .7 %-l juhtudest.

Kahel meie poolt uuritul esines pärast proksimaalset vagotoomiat retsidiivhaavand, mis oli seotud ainult maokorpuse allosas suure kõveriku pool suhteliselt väikese säilinud vaagusinnervatsiooni alaga.

P. E. Donahue ja kaasautorid seostavad seda EKPT alusel sellise vaagusinnervatsiooniga, mis kulgeb mööda parem- ja vasakpoolset *a. gastroepiploica*'t maokorpusele (5). Seetõttu soovitavad nad ka need uitnärvikiud läbi lõigata lisaks tavalisele vagotoomiale ehk teha nii-öelda laiendatud proksimaalne vagotoomia. Seevastu J. Braghetto ja kaasautorite prospektiivsed maosekretsiooni uuringud ei tõestanud erinevust tavalise ja laiendatud proksimaalse vagotoomia vahel (2).

Esitatust nähtub, et insuliintesti ja õige 12-tunnise maohappesuse reduktsiooni testiga võrreldes on EKPT vagotoomia täielikkuse hindamisel palju tundlikum ja täpsem. EKPT annab lühikese ajaga ülevaate söögitoru, mao ja duodeenumi limaskesta seisundist ning säilinud vaagusinnervatsiooniga alade lokalisatsioonist ja suurusest. Seepärast tuleb vagotoomia täielikkuse hindamisel ja retsidiivhaavandi diagnoosimisel ning prognoosimisel eelistada kvantitatiivsetele maohappesuse määramise testidele EKPT-d.

KIRJANDUS: 1. *Bank, S., Marks, I. N., Locew, I. H.* Gut, 1967, 8, 38—41. — 2. *Braghetto, I., Csendes, A., Lazo, M.* a.o. Am. J. Sur., 1988, 155, 443—446. — 3. *Glark, C. G., Murray, I. G. I. R.* Coll. Sur. Edinb., 1963, 8, 212—218. — 4. *Cowley, D. I., Spencer, J., Baron, J. H.* Br. J. Surg., 1973, 60, 7, 517—522. — 5. *Donahue, P. E., Bombeck, C. T., Yoshida, Y.* a.o. Am. J. Sur., 1987, 153, 249—255. — 6. *Donahue, P. E., Maroske, D., Rocher, D. H.* a.o. Zenbl. Chir., 1987, 112, 1208—1215. — 7. *Dragstedt, L. R., Harper, P. V., Tovee, E. B.* a.o. Ann. Surg., 1947, 126, 687—708. — 8. *Jordan, P. H. Jr., Condon, R. E.* Ann. Surg., 1970, 172, 547—563. — 9. *Kusakari, K., Nyhus, L. M., Gillison, E. W.* a.o. Arch. Surg., 1972, 105, 386—391. — 10. *Kyaergaard, I., Jensen, H.-E., Allermand, H.-E.* Ann. Sur., 1980, 192, 6, 711—715. — 11. *Lunde, O. Ch., Liavåg, I., Roland, M.* World J. Surg., 1983, 7, 751—756. — 12. *Lyndon, P. I., Greenall, M. I., Smith, R. B.* a.o. Gastroenterology, 1975, 69, 1188—1195. — 13. *Macintyre, I. M. C., Millar, A., Smith, A. N.* a.o. Br. J. Surg., 1990, 77, 65—69. — 14. *Paimela, H., Ahonen, J., Höckerstedt, K.* a.o. Ann. Chir. Gynaecol., 1983, 72, 3—8. — 15. *Saik, P. R., Greenburg, A. G., Peskin, G. W.* Am. J. Sur., 1982, 144, 518—522. — 16. *Stempien, S. I., Dagardi, A. E., Seifer, H. W.* Proceedings World Congress Gastroenterology (Washington), 1958, 1026—1034.

Summary

Postoperative Endoscopic Congo Red Test for estimating the completeness of vagotomy. According to Endoscopic Congo Red Test (ECRT) in 271 duodenal ulcer patients the vagotomy was found to be incomplete in 50% of the cases averagely 8 years after the operation. The vagotomy is incomplete more often after proximal vagotomy (PV) than after truncal vagotomy (TV), 56% and 34% respectively ($p<0.001$). The incomplete vagotomy areas were localized in 82% of the cases after PV and even more often after TV in the upper part and in 33% of the cases in the lower part of the gastric corpus mucosa. 18 recurrent ulcers from 19 were connected with the incompleteness of vagotomy. They were more frequent in large incomplete vagotomy areas involving 20% or more of the gastric corpus mucosa. ECRT is more exact and informative for estimating the completeness of vagotomy than the insulin test and the nocturnal 12-hour gastric secretion reduction test.

Submitted for publication

RISK EVALUATION OF POSTVAGOTOMY ULCER RECURRENCE BY USING ENDOSCOPIC CONGO RED TEST AND GASTRIC SECRETION TESTS

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Peetsalu A, Härkönen M, Peetsalu M, Vardja T, Villako K & Varis K. Risk Evaluation of Postvagotomy Ulcer Recurrence by Using Endoscopic Congo Red Test and Gastric Secretion Test. Scand J Gastroenterol 1992.

The possibilities to discriminate cases with postvagotomy recurrent ulcer by using endoscopic Congo Red test (ECRT), gastric acid secretion tests and serum pepsinogen I (S-PGI) were compared in 39 duodenal ulcer (DU) patients 5-12 years after vagotomy. The patients were selected from 270 operated DU patients. ECRT was positive in 135 cases (50%), and 18 of them (13%)had a recurrent ulcer. Only one case of 135 with a negative ECRT had a recurrent ulcer. The 39 patients were classified in two main groups. Group A consisted of 13 patients with a postoperative recurrent ulcer, and with positive ECRT. Group B consisted 26 cases without recurrent ulcer, and was classified in two subgroups according to the ECRT. Group B1 consisted of 13 patients with a positive ECRT, and group B2 of 13 patients with a negative ECRT. Basal acid output (BAO), maximal acid output (MAO), and nocturnal acid output (NAO) were determined pre-and postoperatively. ECRT, insulin test and S-PGI were determined only postoperatively. Positive ECRT had 95% sensitivity and 53% specifity for postvagotomy DU-recurrence. S-PGI>150 µg/l had the highest specifity (92%), but only 54% sensitivity. The sensitivity of a combination of a positive ECRT and S-PGI > 150 µg/l was 100%. The mean postoperative decrease of BAO was 56% in group A, and 84% in group B ($p<0.05$). The respective figures for MAO were 52% and 69%, and for NAO 55% and 78% ($p<0.05$). The insulin test showed 83% sensitivity and 78% specificity for ulcer recurrence. The respective figures for the combination of BAO>1.5 mmol/h with NAO>30 mmol/12 h were 80% and 81%. We conclude that ECRT should be the primary step for estimating postvagotomy ulcer risk, and further gastric secretion studies, such as S-PGI and BAO+NAO or insulin test are needed only in ECRT-positive cases.

Key words: Duodenal ulcer, vagotomy, recurrent ulcer, insulintest, endoscopic Congo Red test, serum pepsinogen I, basal, acid output, maximal acid output, nocturnal acid output.

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Highly selective vagotomy (proximal vagotomy) has been proved to be an effective method in controlling the course of duodenal ulcer disease, and in preventing of recurrent ulcers. However, a part of operated patients will get an ulcer relapse in spite of test results indicating a successful vagotomy. Repots from different centres indicate that about 10-25% of duodenal ulcer patients will get a recurrent ulcer during 5-15 years follow-up after a highly selective vagotomy (1), whereby the risk evaluation of recurrent postoperative ulcer would be important.

The sensitivity, specifity, predictive value and discriminatory ability of gastric secretion tests based on pentagastrin stimulation or insulin hypoglycaemia are poor both after truncal and selective vagotomy (for references see: 2). Basal acid output (3) and nocturnal acid output (4) seem to be more useful in the evaluation of ulcer risk after vagotomy. However, gastric tests which are based on the collection of gastric juice by a nasogastric tube are inconvenient. Serum pepsinogen I (S-PGI) reflects the secretion of the gastric corpus mucosa, and it tends to be higher in patients with postvagotomy recurrent ulcer (5). Endoscopic Congo Red test (ECRT) shows the location and size of the residual innervation area in the gastric corpus mucosa after vagotomy, and may be a more reliable indicator of risk of recurrent ulcer than many acid secretory tests (6). Small areas of residual innervation may not be clinically important, whereas if areas greater than 20% are involved, recurrent ulcer can be expected to occur in 40% of cases within two years (6). Insulin test has been during decades the classic method to examine the completeness of vagotomy. However, it is a time wasting and inconvenient procedure, whereas ECRT is an easy and quick visual method to evaluate the residual acid secretion capacity at gastroscopy.

There is no generally accepted policy in the estimation of recurrent ulcer risk after vagotomy. The aim of this study was to evaluate the usefulness of ECRT, and to compare the sensitivity and specificity of diffenent tests in the discrimination of cases with high risk for postvagotomy ulcer.

SERIES AND METHODS

Patients

The patient series consisted of 39 patients with duodenal ulcer, who had undergone vagotomy in 1976-1984 at the Second Department of Surgery, University of Tartu, Estonia. A proximal vagotomy performed in 30 cases (15 with pyloroplasty, and 6 with duodenoplasty), and a truncal vagotomy with pyloroplasty in 9 cases.

The patients were selected from 270 duodenal ulcer patients, who were examined by gastroscopy, ECRT (7) and extensive gastric secretion tests 5-12 years after vagotomy. ECRT was positive in 135 cases (50%), and 18 of them (13%) had a recurrent ulcer. Only one case from 135 patients with a negative ECRT result had a recurrent ulcer.

Group A consisted of 13 patients with recurrent ulcer and positive ECRT.

Group B consisted of 26 patients without recurrent ulcer at control endoscopy. They were selected for each case in group A to have two control patients of same age and of the same type of gastric operation. In all control pairs one patient had positive and the other negative ECRT. Thirteen control patients with positive ECRT formed group B1, while group B2 consisted of 13 control patients with negative ECRT.

The details of both groups is presented in Table I.

Table I. The characteristics of patient group A with postvagotomy ulcer, and patient group B without postvagotomy ulcer.

	Group A	Group B
Number of cases	13	26
Male/Female	10/3	25/1
Age (years)(mean ± SE)	47.8 ± 3.1	49.0 ± 1.8
Follow-up time (years) (mean ± SE)	8.1 ± 0.6	8.0 ± 0.4

Methods

Examinations performed in all patients in group A and B are listed in Table II.

Table II. Examinations performed in 39 patients during the study.

	Preoperative (No. of examined)	After 5-12 years follow-up (No. of examined)
Gastroscopy	39	39
ECRT		39
S-PGI		39
BAO	33	30
MAO	34	30
NAO	32	27
Insulin test		30

Gastroscopy

Gastroscopy was performed in the usual manner by using the Olympus GIF-Q scope for all patients in groups A and B 5-12 years after vagotomy irrespective of the abdominal symptoms. Two patients in the group A, and 10 patients in the group B had no abdominal symptoms at the time of endoscopy.

Endoscopic Congo Red Test (ECRT)

Endoscopic Congo Red Test (ECRT) was performed according to Donahue et al. (7) under basal conditions. After aspirating all gastric contents, solution of 0.5% Congo Red and 5% bicarbonate was sprayed through the endoscope to cover the gastric corpus mucosa. Any area of the mucosa which turned black-blue (pH<3.0) within the first 2-3 minutes was considered positive. This reaction is called "rapid acid secretion". A totally red coloured mucosa after 3 minutes (pH>3.0) was considered a negative test result.

Serum Pepsinogen I (S-PGI)

S-PGI was determined using a radioimmunologic method in the Department of Clinical Chemistry of Helsinki University Central Hospital (8). The serum samples were stored at -20°C before the use. The S-PGI 50-150 µg/l was considered as the normal range.

Gastric acid

Samples for the determination of gastric acid secretion parameters were collected with a nasogastric tube using continuous aspiration. The position of the tube was checked by x-ray.

Basal acid output (BAO) was determined from a gastric juice sample collected during 60 minutes under basal conditions after an overnight fast. The normal range of BAO values is 1-5 mmol/h.

Maximal acid output (MAO)was determined from a gastric juice sample collected during 60 minutes suction after 6 µg/kg Pentagastrin s.c. stimulation of the gastric acid secretion. The normal reference values for MAO are 16-24 mmol/h.

Nocturnal acid output (NAO) was determined from a sample of gastric juice collected during 12 hours between 8 p.m. to 8 a.m. The normal range of NAO is 10-20 mmol/12 h.

Insulin test was carried out by causing insulin hypoglycemia with intravenous insulin 0,2 IU/kg. The test results were interpreted by using a multicriteria analysis. If one of the three criteria (9-11) used was positive, the test result was considered positive.

Statistics

Statistical comparison of test parameters between preoperative and postoperative patient groups was carried out using the Wilcoxon matched-pair signed-rank test. The parameters between postoperative groups were compared using the Mann-Whitney U test. The correlations and the significance of the correlations between gastric acidity and S-PGI were calculated using the Spearman rank correlation.

RESULTS

Prevagotomy secretion patterns

The preoperative gastric acid secretion parameters are presented in Table III. There was no significant difference of the mean values of BAO, MAO and NAO in groups A and B.

Postvagotomy change of acid secretion

The means of BAO, MAO and NAO decreased significantly in all groups (Table III). The mean BAO postoperatively decreased 56% from the preoperative value in group A, and 84% in group B ($p<0.05$). The respective figures for MAO were 52% and 69%, and for NAO 55% and 78% ($p<0.05$).

Postvagotomy secretion patterns

The comparison of postoperative gastric secretion parameters between group A and B indicates the possibility of using these parameters to predict postoperative ulcer risk.

Table III shows the mean postoperative BAO, MAO and NAO in groups A and B. There was no significant difference between the mean of MAO in these groups, whereas the mean BAO and NAO were significantly ($p<0.05$) lower in group B than in group A. The mean postoperative NAO was significantly higher in group B1 than in group B2 ($p<0.05$). The mean postoperative S-PGI was significantly higher in group A than in group B1 ($p<0.05$), whereas there was no significant difference between group A and B2.

The postoperative insulin test was positive in 10 out of 12 (83%) patients in group A, and in 4 out of 18 patients (22%) in group B. The difference between the two groups was significant ($p<0.001$), and a positive insulin test had a 78% specifity for ulcer recurrence.

The sensitivity and specifity of postoperative gastric secretion tests and of some of their combinations in the detection of cases with recurrent ulcer are presented in table IV.

Table III. Pre- and postoperative basal acid output (BAO), maximal acid output (MAO), nocturnal acid output (NAO), and serum pepsinogen I (S-PGI) (mean ± SE, range) in 13 patients with recurrent ulcer after operation (Group A), in 13 patients without postoperative ulcer and with a positive endoscopic Congo Red test (Group B1), and in 13 patients without postoperative ulcer and with a negative endoscopic Congo Red test (Group B2), and in whole control series of 26 patients without recurrent ulcer (Group B).

Test	Preoperative patient groups				Postoperative patient groups			
	A	B	B_1	B_2	A	B	B_1	B_2
BAO (mmol/l)	5.4 ± 1.0	6.1 ± 0.8	6.8 ± 1.4	5.5 ± 0.9	2.4 ± 0.6[1]	1.0 ± 0.3[2,3]	0.9 ± 0.4[2]	1.2 ± 0.4[2]
MAO (mmol/h)	22.0 ± 2.8	20.8 ± 2.2	22.5 ± 2.9	19.5 ± 3.2	10.6 ± 1.8[2]	6.5 ± 1.0[2]	7.0 ±1.7[2]	5.8 ± 3.3[2]
NAO (mmol/12 h)	50.6 ± 7.6	40.1 ± 7.3	44.3 ± 13.2	36.6 ± 8.0	22.8 ± 4.5[1]	9.0 ± 2.1[2,3]	13.8 ± 2.7[1]	3.7 ± 2.0[2,4,5]
S-PG I (µg/l)					146.5 ± 16.2	104.7 ± 7.6[3]	91.0 ± 7.7[6]	118.4 ± 12.3

[1] $p < 0.05$ preoperative vs postoperative
[2] $p < 0.01$ -"- } Wilcoxon

[3] $p < 0.05$ postoperative A vs B
[4] $p < 0.05$ postoperative A vs B_2
[5] $p < 0.05$ postoperative B_1 vs B_2
[6] $p < 0.05$ postoperative A vs B_1 } Mann-Whitney

Table IV. Sensitivity and specifity of secretory tests in the discrimination of patients with recurrent ulcer after vagotomy.

Laboratory test	Sensitivity	Specifity
S-PGI > 100 µg/l	69 %	46 %
S-PGI > 150 µg/l	54 %	92 %
BAO > 1,5 mmol/h	73 %	74 %
MAO > 10 mmol/h	55 %	84 %
NAO > 10 mmol/12 h	73 %	59 %
BAO > 1,5 mmol/h+NAO>30 mmol/12 h	80 %	81 %
Insulin test	83 %	78 %

A high S-PGI>150 µg/l was the most specific test for detecting cases with recurrent ulcer, but the sensitivity of this test is low. The combination of a BAO>1.5 mmol/h and a NAO>30 mmol/12 h showed the greatest accuracy in the detection of recurrent ulcer when both sensitivity and specifity are considered, 80% and 81% respectively. Figures 1 and 2 show the individual values for the combination of postoperative BAO and NAO in groups A and B. Eight cases out of 10 with a recurrent ulcer had a combination of an NAO>30 mmol/12 h and a BAO>1.5 mmol/h (Fig. 1). Only three out of 16 patients without recurrent ulcer had a similar test combination (Fig. 2).

There was a significant positive correlation between individual S-PGI and NAO values in group A (r=0.8061, p=0.0156), whereas this correlation was not seen in group B.

ECRT was positive in 18 out of 19 patients with recurrent ulcer, which gives a sensitivity of 95% for postvagotomy ulcer relapse. Altogether 134 out of 251 patients without ulcer relapse had a positive ECRT, which indicates a low specifity (53%) of ECRT for postvagotomy ulcer recurrence.

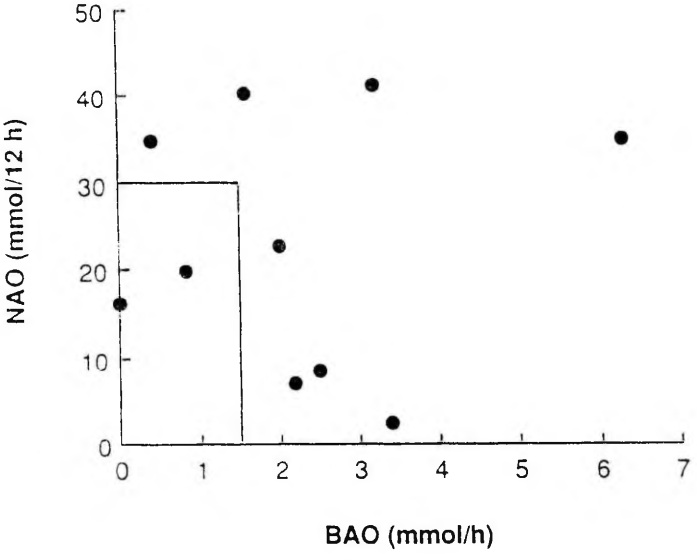

Fig.1 Postoperative BAO (basal acid output) and NAO (nocturnal acid output) in 10 patients with recurrent ulcer. Sensitivity of this test combination is 80%.

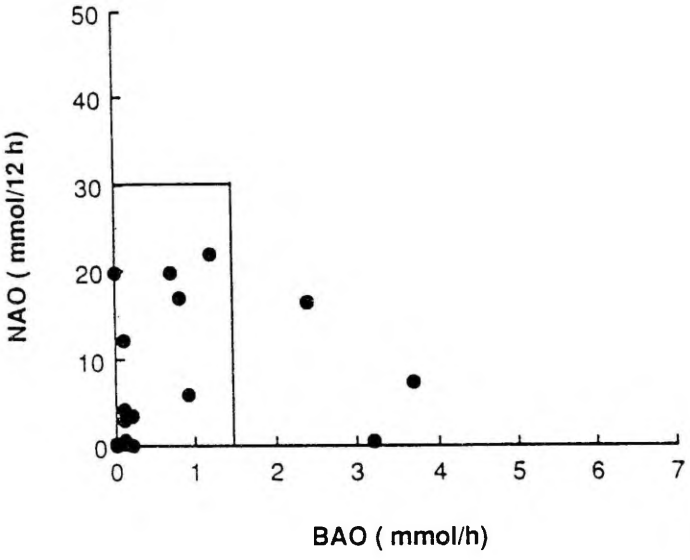

Fig.2 Postoperative BAO (basal acid output) and NAO (nocturnal acid output) in 16 patients without recurrent uloer. Specificity of this test combination is 81%.

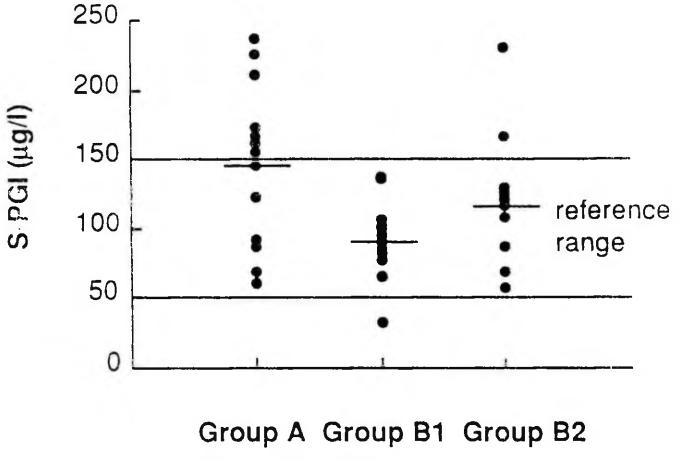

Fig.3 Concentration of serum pepsinogen I (S-PGI) in 13 patients with recurrent ulcer after vagotomy (Group A), in 13 patients without postoperative ulcer and with a positive endoscopic Congo Red test (Group B1), and in 13 patients without postoperative ulcer and with a negative endoscopic Congo Red test (Group B2).

Figure 3 shows the individual values of S-PGI in different patient groups. A high S-PGI>150 µg/l was observed in 7/13 patients (54%) in group A, whereas only two patients out of 26 (8%) in group B had a high S-PGI. This difference is statistically significant ($p<0.05$) whereas there was no significant difference between groups B1 and B2 in this respect. Accordingly, a high S-PGI is specific for detecting ulcer recurrence but its sensitivity is low. In ECRT positive cases, however, the sensitivity of a high S-PGI rises to 100%.

DISCUSSION

To estimate the risk of postvagotomy recurrent ulcer, three technically different methods can be used. Gastric acid secretion parameters need gastric suction, which is time consuming and inconvenient for patient. Especially insulin test may be unpleasant and even risky for elderly patients or for patients with cardiovascular disorders, diabetes etc. A considerable shorter time period will be spent for the ECRT and this is less distressing for the patient. Only a fasting serum sample is required for the determination of S-PGI.

Postvagotomy endoscopy is essential since a certain proportion of ulcer relapses are asymptomatic. This has been shown in our series and in the literature (12). Congo Red staining is an easy and reliable method to evaluate the remaining gastric secretion capacity during a routine endoscopy (6). Accordingly ECRT is only an easy addition to a routine endoscopy and does not need a separate examination.

The essential finding in our study was the reliability of ECRT results in detecting recurrent ulcer 5-12 years after vagotomy. ECRT is primarily characteristic of vagally controlled gastric secretion (13). In our series, nearly all recurrent ulcer patients were ECRT positive. It can be concluded that a high risk of recurrent ulcer postvagotomy is associated with residual vagal innervation in the gastric corpus. As would be expected, in our series ECRT reflected the changes in the NAO, which is primarily vagally controlled. In ECRT positive recurrent ulcer patients the mean NAO was significantly higher than in ECRT negative cases.

From our data a conclusion of high practical importance can be drawn. A negative ECRT excludes the risk of ulcer recurrence after vagotomy with a very high probability. This conclusion is based on our series where 18 (95%) recurrent ulcer cases out of 19 were ECRT positive and only 1 case (5%) was negative. This means that the case of a negative ECRT no further risk studies are necessary. ECRT had a low positive predictive value of 13% for ulcer recurrence. So than further studies for estimating the ulcer relapse risk are required.

The present study shows that the combination of BAO>1.5 mmol/h + NAO>30 mmol/12 h discriminate with about 80% sensitivity and specificity the cases with recurrent ulcer from cases without ulcer recurrence. According to the data in the literature, ulcer recurrence rates do not depend significantly on whether the acid secretion remains high immediately after vagotomy or whether there is an early low secretion output which increases over time (14). To estimate the recurrent ulcer risk, repeated BAO and NAO may prove necessary for determining the gastric acid secretion level and its rise during the follow-up period. In practice, however, the use of these tests is limited because they are distressing for the patient.

In our series, the insulin test also showed a relatively high sensitivity and specificity for recurrent ulcer risk, 83% and 78%, respectively. Such a high specificity can here be attributed to the selected subjects in whom the proportion of recurrent ulcers was high (12/30, 40%). In study group with a lower proportion of recurrences, e.g. 23% (15/65) 5 years after proximal vagotomy (15), the sensitivity of the insulin test was 87% whereas its specificity was only 52%, so reducing considerably the value of the test for recurrent ulcer diagnosis. In addition , the insulin test is more difficult for the patient to endure and may inour complications (16).

The sensitivity and specificity of other gastric acid secretion parameters in the discrimination of postvagotomy recurrent ulcer is lower. This wiew is supported by data in the literature (12) although recurrent ulcer patients have a higher mean BAO and MAO values than those without ulcer relapses (1,17) as also confirmed by our data.

A simple and relatively non-invasive method for the patient is S-PGI which correlates with the basal and stimulated output of pepsinogen secreted into the gastric lumen (18). It has been reported earlier that, for clinical purposes, S-PGI is not useful for evaluating the "severity" of duodenal ulcer in those patients who have not had surgical treatment for DU (19). Nevertheless, high S-PGI values have been helpful in selecting patients who should receive maintenance therapy for recurrence prophylaxis (20).

In our series 5-12 years after vagotomy the mean S-PGI in patients with recurrent ulcer was significantly higher than in those without recurrence as has also been reported earlier (21). This study shows that an S-PGI>150 µg/l was the most specific test for detecting ulcer relapse, but its sensitivity is low. Our patient series demonstrate that in the presence of ulcer recurrence the sensitivity of high S-PGI>150 µg/l increases to 100% when the ECRT is positive. In ECRT negative cases high S-PGI values were not discriminatory in this respect. Earlier it has been shown that there is no correlation between BAO and S-PGI (22), or between peak acid output and S-PGI (23), either before or after vagotomy. We found a significant positive correlation between the S-PGI and NAO values in patients with recurrent ulcer while such correlation was absent in other patients. It means that after vagotomy there is some correlation between higher acid output and higher S-PGI values whereas there is no such correlation in cases of low values of acid output. Therefore, both gastric acid secretion and S-PGI must be considered together in order to suspect postvagotomy ulcer recurrence.

Analysing the results of the three different methods, one can see that no single method exists which is both of high sensitive and specific for estimating the recurrent ulcer risk and at the same time is endured easily for the patient. Hence, these methods must be combined. The present study shows that it is expedient to start with ECRT. It is a relatively quick and highly sensitive method. If ECRT is negative, the development of recurrent ulcer is unlikely and no further studies along these lines are necessary. If ECRT is positive, BAO, NAO and

S-PGI must be determined. In cases where BAO>1.5 mmol/h + NAO>30 mmol/12 h, or S-PGI>150 µg/l there is a high risk of ulcer relapse. Since S-PGI is easier for the patient, it should be preferred to BAO and NAO. Repeated S-PGI during the follow-up period for detecting patients with recurrent ulcer risk may make it possible to avoid relapses by timely preventive therapy.

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REFERENCES

1. Macintyre IM, Millar A, Smith AN, Small WP. Highly selective vagotomy 5-15 years on. Br J Surg 1990,77,65-69.
2. Baron JH. Clinical tests of gastric secretion. The Macmillan Press LTD, London, 1978,186-211.
3. Holst-Christensen J, Hansen OH, Pedersen T, Kronborg O. Recurrent ulcer after proximal gastric vagotomy for duodenal and pre-pyloric ulcer. Br J Surg 1977,64,42-46.
4. Dragstedt LR, Harper PV, Tovee EB, Woodward ER. Section of thr vagus nerves to the stomach in the treatment of peptic ulcer; complications and end results after 4 years. Ann Surg 1947,126,687-708.
5. Samloff IM, Secrist DM, Passaro E. Serum group I pepsinogen levels and their relation to gastric acid secretion in patients with and without recurrent ulcer. Gastroenterology 1976,70,309-313.
6. Saik RP, Greenburg AG, Peskin GW. The Congo Red Test to determine completeness of vagotomy. Am J Surg 1982, 144, 518-522.
7. Donahue PE, Maroske D, Roeher DH, Nyhus LM. Experience with the endoscopic test for completeness of vagotomy. Results of application in two medical centers. Zentrbl Chir 1987,112,1208-1215.
8. Tamm A, Villako K, Harkonen M, Karonen S-L. Serum pepsinogen I and the state of gastric mucosa in an Estonian population sample. Scand J Gastroenterol 1984, 19, 1091-1094.

9. Stempien SI, Dagardi AE, Seifer HW. Status of duodenal ulcer patients five year or more after vagotomy- pyloroplasty. Proc Word Congr, Gastroenterology, Washington 1958,1026-1034.
10. Clark CG, Murray IG. The Burge test for complete vagotomy. I R Coll Surg Edinb 1963,8,212-218.
11. Bank S, Marks IN, Looew IH. Histamine-and insulin-stimulated gastric acid secretion after selective and truncal vagotomy. Gut 1967,8,38-41.
12. Raab M, Said S, Hilgers RD, Pichlmaier H. Long-term results of high selective vagotomy for the treatment of duodenal ulcer. Hepato-gastroenterol 1989,36,357-362.
13. Donahue PE, Bombeck TC, Yoshida I, Nyhus LM. The simplified Endoscopic Congo Red Test for completeness of vagotomy. Surg Gynaec Obstet 1986,163,297-298.
14. Butterfield DI, Whitfield PE, Hobsley M. Changes in gastric secretion with time after vagotomy and the relationship to recurrent duodenal ulcer. Gut 1982,23, 1055-1059.
15. Lunde O-C, Liavåg I, Roland M.Recurrent ulceration after proximal gastric vagotomy for duodenal ulcer. World J Surg 1983,7,751-756.
16. Feifel G, Falkenberg P, Kemkes B, Geier E. Die Problematik des Insulin-Tests als postoperative Vagotomie Kontrolle. Münch Med Wschr 1974,116,995-1000.
17. Graffner H, Liedberg G, Oscarson I. Acid secretory tests in peptic ulcer disease before and after parietal cell vagotomy. Scand J Gastroenterol 1986,21,41-46.
18. Waldum HL, Burhol PG, Straume BK. Serum group I pepsinogens and gastrin in relation to gastric H^+ and pepsin outputs before and after suboutaneous injection of penta gastrin. Scand J Gastroenterol 1978.13,943-946.
19. Samloff IM, Taggart RM. Pepsinogens, pepsins and peptic ulcer. Clin Invest Med 1987,10,3,215-221.
20. Sumii K, Inabe A, Uemura N, Kimura M, Naruma K, Yoshihara M, Toshima H, Kajiyma G, Miyoshi A. Increased serum pepsinogen I and recurrence of duodenal ulcer. Scand. J Gastroenterol 1989,24,1200-1204.

21. Stabile BE, Passaro EI, Samloff IM, Walsch IA. Serum pepsinogen I, serum gastrin and gastric acid output in postoperative peptic ulcer.Arch Surg 1978,113,1136-1141.
22. Peetsalu A, Tamm A, Härkönen M, Varis K, Sipponen P, Karonen S-L, Väli T, Villako K. The effect of vagotomy and antrectomy in serum pepsinogen I and II. Scand J Gastroenterol 1990,25,455-461.
23. Feldman M, Blair AI, Richardson CT, Samloff IM. Effect of proximal gastric vagotomy on serum pepsinogen I and II concentrations and acid secretion in duodenal ulcer patients. Dig Dis Sci 1988,33,7,824-827.

Curriculum vitae

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