Effect of fundic distension on gastric acid secretion in man

U GRÖTZINGER, S. BERGEGÅRDH, AND L. OLBE

From the Department of Surgery II, University of Göteborg, Sahlgren's Hospital, Göteborg, Sweden

SUMMARY The effect of distension of the fundus and body of the stomach on gastric acid secretion was studied in 26 patients with duodenal ulcer and six healthy subjects. Graded distension produced by inflating a rubber balloon to volumes of 150, 300, and 600 ml resulted in significant sequential increments of acid output. The secretory response outlasted stimulation by at least one hour. In both groups of subjects, the highest acid output obtainable with fundic distension amounted to just above 50% of the maximum secretory response evoked by intravenous infusion of pentagastrin. A significant correlation was found between the peak secretory rates observed during fundic distension and after pentagastrin stimulation. It is concluded that distension of the oxyntic gland area in man is a potent stimulus for gastric secretion of acid and that patients with duodenal ulcer are no more sensitive to this stimulus than healthy subjects.

Food reaching the stomach stimulates the parietal cells to secrete hydrochloric acid by virtue of its physicochemical properties—that is, by activating enteroceptors which are susceptible to chemical and mechanical stimuli. In the dog, mechanical stimulation by gastric distension brings about acid secretion by means of two mechanisms: direct neural activation of the oxyntic glands and pH-dependent release of antral gastrin (Grossman, 1967). This basic concept of dual reflex action applies to both antral and fundic distension (Grossman, 1961, 1962; Debas et al., 1974; Debas et al., 1975). In man, the acid response to the ingestion of test meals has been extensively studied (Hunt and Macdonald, 1952; Rune, 1966; George, 1968; Cooke, 1970; Fordtran and Walsh, 1973; Malagelada et al., 1976). This integrated secretory response is influenced by factors including psychic stimulation, the volume and composition of the meal, the rate of gastric emptying and the effects of chyme on the intestine. Only sparse information is available on the acid secretory effect of the different components which constitute the gastric phase in man. Recent work has shown that antral distension stimulates acid secretion in patients with duodenal ulcer by way of a mechanism which is pH-independent and not mediated by gastrin (Bergegårdh et al., 1975, 1976b). In contrast, healthy subjects did not respond to antral distension.

In the present study, the acid secreting part of the stomach was distended with a balloon and the effect of graded fundic distension on acid secretion was examined in patients with duodenal ulcer and in healthy subjects.

Methods

SUBJECTS STUDIED

Patients with duodenal ulcer (DU) Twenty-six male subjects (mean age 44 years, range 20-63 years) with chronic duodenal ulceration awaiting elective surgery were studied. The diagnosis was established by endoscopy and/or barium meal examination and confirmed at operation. In no patient was there any evidence of gastric outlet obstruction.

Healthy subjects Six healthy men (mean age 23 years, range 20-25 years) without any history of gastrointestinal disease or other relevant illness volunteered to enter the study. Care was taken to inform each subject about the purely scientific interest of the experiments and informed consent was obtained. The investigation has been approved by the Ethical Committee of the Faculty of Medicine, University of Göteborg.

EXPERIMENTAL PROCEDURES

Determination of gastric acid output Pentagastrin infusion and fundic distension experi-
phenol red could be detected, demonstrating the efficiency of the suction system. This indicates that only a minimal volume of fluid was present in the stomach at any particular time.

The continuously aspirated gastric contents were divided into 15-minute samples and the volume and pH were recorded. The amount of acid recovered was determined by titrating 100-ml aliquots to pH 7-0, using 0-1 mol/l NaOH in a Radiometer Autoburette. The phenol red concentration was measured in 4-ml aliquots using a Beckman spectrophotometer at wave length 565 nm after filtration (Millipore filter 1-2 μm) and alkalinisation with a few drops of concentrated NaOH. The percentage recovery of phenol red could thus be estimated for each 15-minute sample. On the assumption that homogeneous mixing had been achieved, the amount of acid secreted could be calculated. All results given below are corrected for pyloric losses. The available data did not permit us to make allowance in these calculations for duodenal-gastric reflux.

Fundic distension

A thin-walled rubber balloon was attached to the nasogastric tube 20 cm from its tip and connected with a thin polyethylene tube which was snugly tied to the nasogastric tube (Fig. 1). The balloon could be inflated with air, volume changes being produced over a five-minute period using a 100 ml syringe. Each balloon assembly was tested for leaks before the experiment and by checking the amount of air withdrawn when distension was released. The balloon was easily identified by fluoroscopy and its position was frequently checked throughout the test. The subjects were encouraged to take an occasional deep breath or to slightly change position. One additional aspiration hole was cut in the nasogastric tube, interrupting its radio-opaque thread. This hole was sited just below the oesophagogastric junction, its positon being verified by fluoroscopy. With these measures, any pooling of gastric contents between the inflated balloon and the stomach wall could be minimised. During distension, the percentage marker recovery was not higher than under basal conditions and was in agreement with the values observed in antral balloon distension experiments (Bergegårdh and Olbe, 1975).

In pilot studies, it was found that distension volumes of 800 or 900 ml regularly induced epigastric fullness, pain or even nausea and occasionally retching. In the presence of these symptoms the acid output was markedly depressed. The volumes chosen for the study were generally well tolerated. A few subjects experienced discomfort during the experiment and these results were excluded. In two patients with DU, intrinsic balloon pressure was
Effect of fundic distension on gastric acid secretion in man

Fig. 2 The acid secretory pattern induced by fundic distension in 26 patients with DU. Means in mmol/15 min. The vertical bars indicate the standard errors of the means.

continuously monitored using a Statham transducer and recorded on a Mingograph. The pressure exerted on the gastric wall did not exceed 15 cm H₂O and did not rise with increasing distension volumes.

Basal acid output was recorded during at least 45 minutes. The balloon was then inflated to volumes of 150, 300, and 600 ml, each level of distension being maintained for one hour. After distension had been released, acid secretion was collected for another hour. The mean value of the last two 15-minute periods under basal conditions, during distension with 150, 300, and 600 ml, and in the post-distension period, was taken to represent the acid output during the corresponding step of the experiment. The mean of the two highest subsequent 15-minute values observed at any time during distension denotes the peak acid output produced by fundic distension (PAO₉₅₅).

Pentagastrin infusion
Basal secretions were collected for one hour. Pentagastrin (Peptavlon, ICI) was then infused intravenously in a dose of 90 µg/h for 45 minutes followed by 300 µg/h for a further 60 minutes. The peak acid output after pentagastrin stimulation (PAO₉₅₅₆) was defined as the mean of the two highest consecutive 15-minute values. Dose-response studies performed in this laboratory (Bergegärdh et al., 1976a) have shown that the observed PAO₉₅₅₆ amounts to roughly 90% of the calculated maximal response to intravenous pentagastrin or betazole and may serve as an approximation for the maximal secretory capacity.

Statistical evaluation
In both groups of subjects the individual values of the different steps of the experiment were compared on a computer by analysis of variance for paired data followed by the multiple comparison technique of Scheffé (Morrison, 1967). Correlations were examined by regression analysis. Student's t test and the Mann-Whitney U-test were used when appropriate.

Results
Patients with DU
In 26 patients with DU, graded fundic distension uniformly caused a prompt rise in the secretory rate, which then levelled off and was reasonably stabilised during the last two 15-minute periods at each distension volume (Fig. 2). When distension was released, the acid output decreased rapidly but did not fall to

Table Gastric acid responses to graded fundic distension and to intravenous pentagastrin in 26 patients with DU and six healthy subjects (means ± SD, mmol/15 min)

<table>
<thead>
<tr>
<th></th>
<th>DU patients</th>
<th>Healthy subjects</th>
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<tbody>
<tr>
<td>Basal</td>
<td>1.7 ± 1.1</td>
<td>1.7 ± 1.5</td>
</tr>
<tr>
<td>Distension (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>2.8 ± 1.4</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>300</td>
<td>4.4 ± 1.9</td>
<td>3.5 ± 1.5</td>
</tr>
<tr>
<td>600</td>
<td>5.6 ± 2.0</td>
<td>5.0 ± 1.6</td>
</tr>
<tr>
<td>Post-distension</td>
<td>3.6 ± 1.7</td>
<td>3.3 ± 1.1</td>
</tr>
<tr>
<td>PAO₉₅₅₆</td>
<td>5.9 ± 2.1</td>
<td>5.3 ± 1.3</td>
</tr>
<tr>
<td>PAO₉₅₅₆, 100</td>
<td>11.0 ± 2.5</td>
<td>10.9 ± 2.0</td>
</tr>
<tr>
<td>PAO₉₅₅₆, 100</td>
<td>53.3 ± 14.5</td>
<td>50.1 ± 15.8</td>
</tr>
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basal levels within the observation time, showing that the response outlasted stimulation. Mean basal secretion was 1·7 mmol/15 min. Fundic distension with 150, 300, and 600 ml lead to significant ($p < 0·01$) sequential increments in acid output with mean values of 2·8, 4·4, and 5·6 mmol/15 min, respectively (Table, Fig. 3). The post-distension secretory rate (mean 3·6 mmol/15 min) was significantly ($p < 0·001$) different from both basal acid output and 600-ml response. The individual peak acid responses were usually observed during distension with 600 ml (in 23 out of 26 patients, and during 300-ml distension in the remaining three) and averaged 5·9 mmol/15 min, corresponding to 53·3% of the mean PAO$_{pg}$ (11·0 mmol/15 min). The peak responses to fundic distension and pentagastrin infusion were found to be significantly ($r = 0·69$, $p < 0·001$) correlated (Fig. 4).

The pH of the gastric contents was between 2·0 and 2·7 under basal conditions and fell to 1·6-2·0 during distension with 600 ml.

The mean phenol red recovery amounted to 86% under basal conditions, 86, 86, and 85% during distension with 150, 300, and 600 ml, respectively, and rose to 90% in the post-distension hour. In the pentagastrin infusion tests the phenol red recovery averaged 91%.

Healthy subjects
In six healthy young men, graded fundic distension produced a stepwise increase of acid output in a manner which was very similar to that observed in patients with DU, although with 300-ml distension the pattern was somewhat erratic (Fig. 5). Mean basal acid output was 1·7 mmol/15 min. Fundic distension with 150, 300, and 600 ml caused significant ($p < 0·05$) increases to 3·3, 3·5, and 5·0 mmol/15 min, respectively, although the difference between the 150-ml and 300-ml responses was not statistically significant (Table, Fig. 3). The mean post-distension acid output amounted to 3·3 mmol/15 min and was significantly ($p < 0·05$) different from both basal secretion and 600-ml response. With the exception of one case, the highest individual secretory rate was observed during distension with 600 ml. The mean PAO$_{dist}$ was 5·3 mmol/15 min or 50·1% of the peak acid output after pentagastrin stimulation (10·9 mmol/15 min, Table). The relation between the peak responses to fundic distension and to pentagastrin infusion in this small group of subjects is shown in Fig. 4.

The pH of the gastric contents was between 2·1 and 2·9 under basal conditions and fell to 1·6-2·0 during 600 ml distension.

The mean phenol red recovery was 82% during basal, 86, 87, and 88% during distension with 150, 300, and 600 ml, respectively, and 89% post-distension. In the pentagastrin infusion tests, the mean marker recovery amounted to 91%.

No significant differences were found between patients with DU and healthy subjects when comparing either observed secretory values (Table) or
Effect of fundic distension on gastric acid secretion in man

percentage figures after normalisation of the secretory data with regard to the individual PAOpg.

Discussion

The acid secretory response to the ingestion of a meal is the net result of interacting stimulatory and inhibitory mechanisms arising during the cephalic, gastric, and intestinal phases (Lim et al., 1925; Malagelada et al., 1976). Part of the gastric phase is activated mechanically by virtue of the meal volume (Hunt and Macdonald, 1952; George, 1968; Cooke, 1970). Distension of the human stomach brings about reflex mechanisms resulting in acid secretion as well as in gastric receptive relaxation (Jahnberg et al., 1975; Stadaas, 1975) and pancreatic enzyme and water secretion (White et al., 1963). Our knowledge concerning the mechanisms by which distension of either the oxyntic or pyloric gland area activates the parietal cells to secrete acid stems mostly from animal experiments. In the dog, fundic distension entails cholinergic oxynto-oxyntic reflexes running in short intramural and long vagovagal pathways (Grossman, 1961; 1962). Preshaw (1970) demonstrated that the distension response partly depends on the antral pH and on the integrity of antral innervation. Recently, an oxynto-pyloric, probably vagovagal, reflex for release of antral gastrin has been discovered (Debas et al., 1975; Debas and Grossman, 1975).

In the present study, graded fundic distension resulted in volume-related secretory responses in patients with DU as well as in healthy subjects. This is in agreement with the observations of other workers who used liquid test meals distending the whole stomach (Hunt and Macdonald, 1952; Cooke, 1970). Apparently, motor effects were evoked as well. Presumably because of reflex relaxation of the gastric fundus and body (Jahnberg et al., 1975; Stadaas, 1975), the transmural pressure remained unchanged in the two DU patients examined, although the distending volume was quadrupled.

It is recognised that the experimental model used in this study is not really ‘physiological’ in that distension was increased with time, whereas the reverse order of events takes place during the digestion of a meal. It was found that the response uniformly outlasted stimulation, a phenomenon also observed in sham feeding experiments in man (Knutson and Olbe, 1973). Up to one hour after relief of distension, the secretory rate was still of a magnitude corresponding to the response to 300-ml distension. This pattern of prolonged responses precludes the use of diminishing graded distension in a single test.

The application of dose-response data to a suitable kinetic model provides a valuable tool for the determination of stimulant-receptor interactions (Makhlouf, 1973) and allows one to characterise ulcer patients as compared with normal man (Isenberg et al., 1975). Obviously, the precise definition of the stimulant in quantitative and qualitative terms is a prerequisite. Electrophysiological evidence obtained in a number of animals (Paintal, 1954; Iggo, 1955) indicates that distension of the stomach activates slowly adapting tension receptors causing an increased discharge in vagal afferent fibres. These specialised enteroreceptors, probably located in, and ‘in series’ with, the muscularis propria (Iggo, 1957) respond to tangential lengthening of the gastric wall rather than to the distending volume as such (Leek, 1972). Hence, this distension effect is exerted by changes in tension which, according to the law of Laplace is determined by the prevailing transmural pressure, the distending volume, and the geometrical form of the organ. Since the shape of the stomach and the surface under exposure will change during graded balloon distension of the intact organ, the tensions actually generated are difficult to determine. It would be questionable to quantify the stimulus in terms of distending volumes in order to establish a dose-response relationship for acid responses to fundic distension. We did not find any significant differences between healthy subjects and DU patients when comparisons were based on either observed data for acid output or when the responses were normalised with regard to the individual peak acid output after pentagastrin stimulation. This observation may indicate that patients with DU are no more sensitive to fundic distension than normal man. In contrast, patients with DU have been shown to have an increased responsiveness to pentagastrin stimulation (Isenberg et al., 1975) and to antral distension (Bergegåråd and Olbe, 1975).

The observed peak acid response to fundic distension averaged about half the PAOpg in both healthy subjects and patients with DU (Table), showing that mechanical activation of the parietal cell area alone is a potent secretory stimulus in man. Moreover, there was a significant positive correlation between the peak acid outputs during fundic distension and after pentagastrin stimulation in patients with DU. The intercept of the regression line was not significantly different from zero, and its slope indicates that the mean PAOdist amounts to 57% of the mean PAOpg. In agreement with the observations of others (Hunt and Macdonald, 1952; Cooke, 1970) we found in pilot studies that vigorous distension with balloon volumes of 800-900 ml dampened rather than enhanced the secretory rate. This may well be due to non-specific inhibition since the subjects experienced epigastric fullness and pain or nausea.

In the dog, mechanical activation of the pyloric...
antrum is a powerful stimulus for gastrin release and acid secretion (Woodward et al., 1957; Debas et al., 1974). Antral distension fails to stimulate acid secretion in normal man and produces only a moderate response in ulcer patients, apparently without liberation of gastrin (Bergegårdh and Olbe, 1975; Bergegårdh et al., 1976b). In gastric fistula dogs with innervated antral pouches, Preshaw (1970) found that the peak response to fundic distension amounted to 42% of the highest acid output after stimulation with exogenous gastrin. Our findings indicate that mechanical activation of the oxyntic gland area in man is a secretory stimulus at least as potent as in the dog. In contrast with the observations on antral distension, there is no significant difference between normal subjects and patients with DU.

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