MRI for evaluation of gastric physiology

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Chapter 7

Effect of somatostatin on gastric emptying, measured with magnetic resonance imaging, in functional dyspepsia

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Abstract

Delayed gastric emptying has been identified as a possible pathophysiological mechanism in Functional Dyspepsia (FD). The decatetrapeptide somatostatin has numerous effects on the gastrointestinal tract. Controlled data on the effect of somatostatin on gastric emptying are conflicting and data on the effect of somatostatin on postprandial symptoms in FD are lacking.
The aim of this study was to explore in a mechanistic study the effect of somatostatin on gastric volumes, emptying, motility and symptoms in patients with FD and in healthy subjects using Magnetic Resonance Imaging.
Eleven healthy subjects and 11 patients with FD participated in a randomized, placebo-controlled study. The effect of either somatostatin or saline on gastric function was studied on separate days using three-dimensional volume scans and two-dimensional dynamic scans.
Stomach volume was significantly smaller throughout the somatostatin experiment in both FD and health; mean difference of 70 (24) ml and 109 (12) ml respectively. Gastric emptying was delayed in dyspeptics compared to controls: half emptying time 128 ± 22 vs 106 ± 24 min ($p<0.05$). Somatostatin significantly ($p<0.05$) reduced lag time and ninety-minute retention in both groups. Neither postprandial contraction frequency nor dyspeptic symptoms were affected by somatostatin.
We conclude that, measured with Magnetic Resonance Imaging, somatostatin reduces postprandial gastric volumes and contents in controls and dyspeptics through more rapid initiation and through acceleration of gastric emptying without affecting gastric motility. Somatostatin did not result in postprandial symptom reduction in FD patients.

Introduction

Functional dyspepsia (FD) has recently been redefined by the 3rd Rome Committee on Functional Gastroduodenal Disorders as the presence of symptoms thought to originate from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms. More recently a subgroup classification into postprandial distress syndrome and epigastric pain syndrome has been proposed. Typical postprandial symptoms are fullness, early

satiation and nausea (1). Several pathophysiological mechanisms have been identified in FD, such as delayed gastric emptying, hypersensitivity to gastric distension, altered duodenal sensitivity to acid or nutrients, impaired gastric accommodation to a meal or abnormal antroduodenal motility (2-5). Somatostatin is a cyclic tetradecapeptide that is widely distributed throughout the nervous system and the gastrointestinal tract (6). Somatostatin and its long acting synthetic analogue octreotide exert inhibitory effects on gastric acid secretion, pancreatic enzyme secretion and gallbladder and small bowel motility (7). Results of studies on the effect of somatostatin and octreotide on gastric emptying in humans have been conflicting (8-12). While some authors observed an acceleration of gastric emptying by somatostatin in healthy volunteers (11,12), others found evidence for the opposite: an inhibitory effect of somatostatin on gastric emptying (8-10). Both somatostatin and octreotide reduce perception to mechanical and chemical stimuli in the upper gastrointestinal tract and may therefore have potential in the treatment of dyspeptic symptoms (13,14). Mertz et al. (15) found a decreased compliance of the proximal stomach and an increased threshold for fullness in response to octreotide in healthy subjects. Mearadji et al. (13) observed a reduction in visceral perception in healthy subjects, but found no effect on compliance of the proximal stomach. Data on the effect of either somatostatin or octreotide on postprandial distress type FD and gastric emptying are lacking. In recent years, Magnetic Resonance Imaging (MRI) has become available as a noninvasive alternative technique to study gastric volume changes, gastric emptying and motility simultaneously (16-19). Aim of the present study was to explore in a mechanistic study the effect of somatostatin on gastric volumes, emptying and motility simultaneously in both healthy subjects and patients with FD using MRI.

Materials and methods

Subjects

Eleven patients with FD (4 men, 7 women; mean age 44 years; range 28-62 years; BMI 24.4 ± 3.3 kg/m^2) and eleven healthy subjects (6 men, 5 women; mean age 25 years; range 19-51 years; BMI 22.4 ± 3.0 kg/m^2) participated in the study. Patients were selected from the outpatient clinic, fulfilled criteria for FD and all had meal

related symptoms (postprandial distress subgroup). None of the healthy subjects had a history of gastrointestinal disease or abdominal surgery and none was taking medication known to influence gastrointestinal motor and sensory function. The Medical Ethics Committee of our institution had approved the protocol and written informed consent was obtained from each subject.

Study design

In this randomized, single blind, placebo-controlled study each subject participated in two experiments performed on separate occasions with an interval of at least 6 days. Subjects were studied after at least 10 hours of fasting. A cannula was placed in the antecubital vein of one forearm for infusion of either somatostatin (Somatostatin UCB, UCB Pharma BV, Breda, The Netherlands) or saline. Infusion of either somatostatin (250 μg/h) or saline was started 10 min prior to the start of the experiment. The subject was positioned in the MRI scanner and initial scans were performed to determine geometric position of the stomach. The subject was studied in a semi-supine, right side down position (30°) and remained within the MRI scanner throughout the experiment. The experiment started with a three-dimensional volume scan and a two-dimensional dynamic scan. Hereafter, a liquid meal (600 kcal), consisting of homogenized banana (100 g), cream (100 ml), syrup (15 ml), dextrose (10 g) and water (total volume 400 ml) was provided. This high-caloric, fat rich meal was chosen to enable provocation of symptoms in FD patients. The meal was labeled with a paramagnetic MRI contrast agent, meglumine gadoterate (Dotarem®, Laboratoire Guerbet, CdG Cedex, France) (20). The subject was asked to consume the meal within 10 min. After consumption of the meal a volume scan and dynamic scan were performed every 15 min until 90 min after consumption of the meal. Following each dynamic scan, symptoms were scored on a self-report 10-point scale. The subject was instructed to rate symptoms of nausea, epigastric discomfort, fullness and abdominal tension on a scale ranging from 0 (no symptom) to 10 (maximum symptom).

Magnetic Resonance Imaging

All images were obtained using a 1.5T MRI scanner (ASC-NT; Philips Medical Systems, Best, The Netherlands) and a 4-channel SENSE body coil. A volume

scan (20 slices, thickness 10 mm, slice gap 0.00 mm, echo time 3.5 ms, repetition time 10.00 ms, flip angle 25°, field of view 450.00 mm, matrix 256x256 pixels, total acquisition time 30 sec) was performed to determine momentary volumes. A dynamic scan (semi-coronal slice orientation, slice thickness 10 mm, echo time 3.6 ms, repetition time = 10 ms, flip angle 25°, field of view 450mm, matrix 256x128 pixels, 300 images with a temporal resolution of 1 sec) was performed to determine gastric motility. These MRI techniques have been used and validated previously (17,18,21).

Data analysis

Intragastric air and contents were identified and outlined manually in all volume images by one observer (I.Z.) using an in-house made interactive software tool (MASS®, Medis, Leiden University Medical Center, The Netherlands). Volumes were calculated by adding the calculated surfaces of all outlined areas multiplied with the slice thickness. Stomach volume was calculated by adding intragastric air and contents volumes. This method has been described and validated previously (17). Several parameters were determined from acquired data: 1) stomach volumes (ml) in the fasting and postprandial state. 2) gastric motility parameters were obtained at 10 equally distributed points perpendicular to the stomach axis. Peristaltic contractions (Fig. 7.1) were detected and their frequency (min-1) was calculated (17,21).
The bi-phasic model by Siegel et al. (23) was used to fit contents data and obtain parameters of gastric emptying. Several parameters were calculated from the fit data. 1) Half-emptying time (min) was defined as the moment that half of the initial intragastric contents had emptied from the stomach. 2) Lag time (min) was defined as the moment at which 5% of gastric contents were emptied from the stomach. 3) Ninety-minute retention (%) was defined as the percentage of gastric contents remaining in the stomach at 90 minutes after meal ingestion.

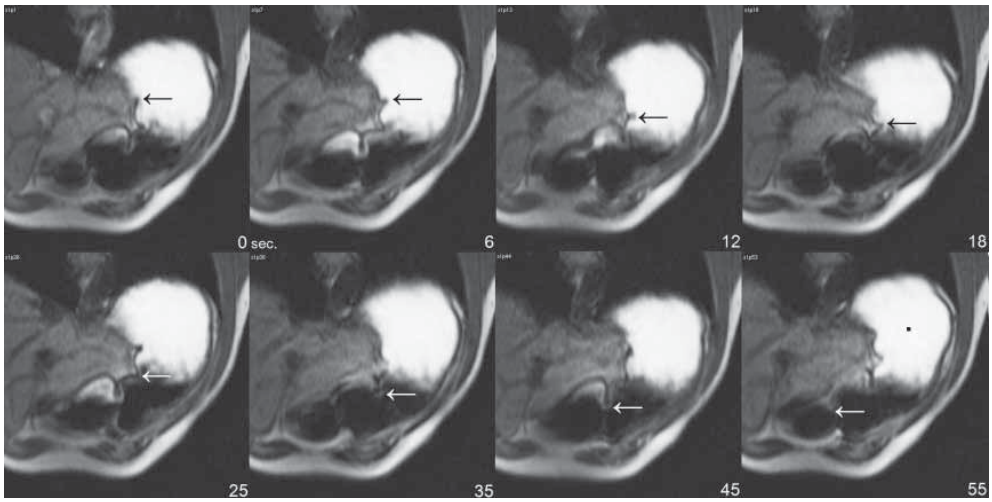

Figure 7.1. Dynamic scan sequence showing peristaltic contractions in the stomach. Peristaltic contractions (arrow) are running from the fundus to the antrum. The gadolinium labeled meal is clearly visible.

Statistical analysis

Data was analyzed using a statistical software package (SPSS® for Windows Release 15.0, SPSS Inc, Chicago, USA). All data is provided as mean ± SD or mean (SE). All samples were tested for normality. Linear mixed model analysis and paired-samples t-test were used to detect differences in data between groups and between the experiments. For linear mixed model analysis data was analyzed in the model using a random subject effect and a fixed time and intervention or group effect. Data was adjusted for multiple comparisons using Bonferroni's correction. The level of significance was set at $p<0.05$.

Results

Gastric volumes

Fasting gastric volumes at t=0 min were not significantly different between FD patients and controls (healthy subjects) neither in the placebo experiment (59 ± 52 vs 68 ± 23 ml) nor in the somatostatin experiment (78 ± 67 vs 56 ± 27 ml). Gastric volumes in FD patients and controls increased significantly upon meal ingestion,

both during placebo and somatostatin and remained increased over basal during the entire study period (Figure 7.2). Throughout the experiment postprandial gastric volumes were significantly smaller for the somatostatin experiment compared to placebo in both FD patients (mean difference 70 (24) ml) and controls (mean difference 109 (12) ml).

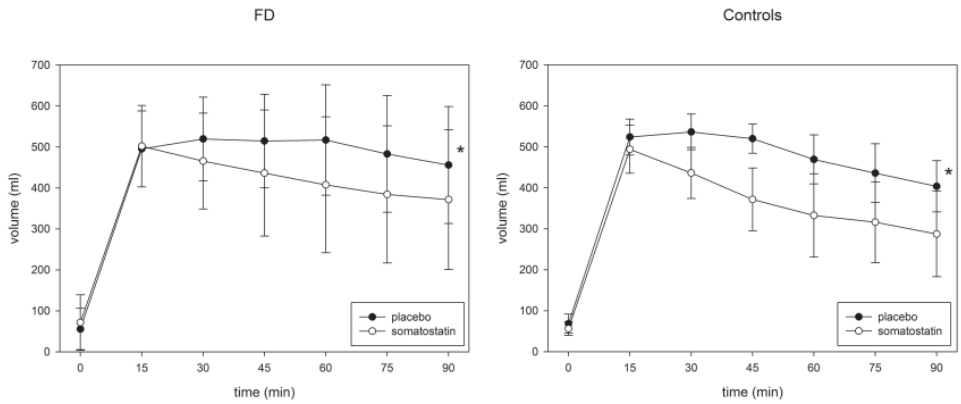

Figure 7.2. Stomach volumes (ml) before and after meal ingestion in FD and controls in response to somatostatin and placebo.
*Values are shown as mean ± SD. * p<0.05 compared to somatostatin throughout the experiment.*

Gastric contents

Figure 7.3 shows the changes in gastric contents during the postprandial period in FD patients and controls both during the somatostatin and the placebo experiment. After meal ingestion, gastric contents increased and thereafter gradually decreased resulting from gastric emptying. The volume of the gastric content was not significantly different between FD patients and controls, neither during the somatostatin nor during the placebo experiment. However, within the groups significant differences in with respect to gastric contents were observed with smaller volumes for the somatostatin experiment compared to the placebo experiment in both FD patients (mean difference 80 (10) ml) and controls (mean difference 77 (12) ml).

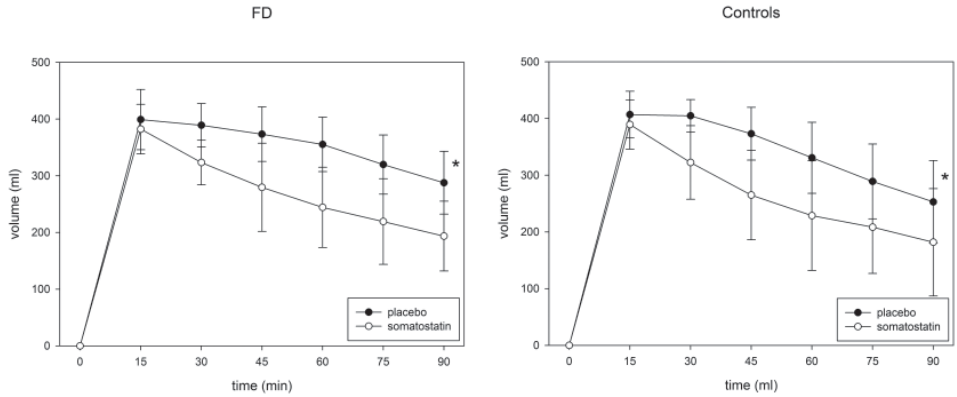

Figure 7.3. Gastric contents (ml) before and after meal ingestion in FD and controls in response to somatostatin and placebo.
*Values are shown as mean ± SD. * $p<0.05$ compared to somatostatin throughout the experiment.*

Data on emptying of gastric contents are given in the Table. Lag time was not significantly different between FD patients and controls, neither during the somatostatin experiment, nor during the placebo experiment. However, somatostatin significantly ($p<0.05$) reduced lag time both in FD patients and controls. Half emptying time was significantly ($p<0.05$) prolonged in FD patients compared to controls during the placebo experiment. In the FD patients half-emptying time decreased significantly during the somatostatin experiment compared to placebo. Half-emptying time between FD patients and controls during somatostatin infusion was in the same range. In the placebo experiments, gastric retention at 90 min was not significantly different between FD patients and controls, but in both groups retention was significantly reduced by somatostatin. The rate of emptying did not differ significantly between FD patients and controls, neither during the placebo experiment, nor during the somatostatin experiment. However, the gastric emptying rate was significantly higher during the somatostatin experiment compared to placebo in FD patients, but not in controls.

	FD		Controls	
	somatostatin	Placebo	somatostatin	placebo
Lag time (min)	15 ± 16*	42 ± 20	16 ± 12*	43 ± 15
T ½ (min)	91 ± 41*	128±22†	89 ± 58	106 ± 24
Retention 90 min (%)	45 ± 18*	70 ± 10	42 ± 23*	60 ± 17
Emptying rate (ml/min)	-4.1± 1.7*	-2.7± 1.1	-3.9±1.9	-3.5±1.0

Table. Gastric emptying data.
*Data are shown as mean ± SD. *p<0.05 compared to placebo. † p<0.05 compared to controls.*

Gastric motility

Gastric contractions are visualized in Figure 7.4. Fasting contraction frequency did not differ significantly between FD patients and controls: neither during the somatostatin experiment, with 14.8 ± 2.1 and 14.4 ± 1.4 contractions per 5 min respectively, nor during the placebo experiment, with 15.0 ± 1.4 and 14.1 ± 1.0 contractions per 5 min respectively. Feeding did not quantitatively affect contraction frequency (data not shown). However, after meal ingestion qualitative changes in motility pattern were observed: the contraction pattern becomes irregular while somatostatin restores the contraction pattern towards a more regular pattern.

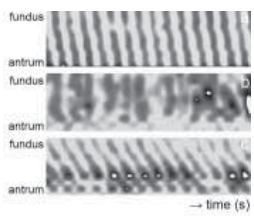

Figure 7.4. Representative contraction pattern of an individual showing 5 min. periods a) prior to meal ingestion, b) after meal ingestion during placebo infusion and c) after meal ingestion during somatostatin infusion. The x-axis shows time and the y-axis shows the location in the stomach from fundus to antrum. Color gradients represent gastric occlusion (darker is more occluded). In a) regular contractions migrate from proximal to distal stomach at a frequency of about 3/min. In b) the frequency is not affected but the pattern (migration) has become irregular. In c) the irregular postprandial pattern is "restored" towards a more regular pattern.

Dyspeptic symptoms

Total symptom scores (range 0-40) were significantly higher in FD patients compared to controls for both experiments (Figure 7.5). After meal ingestion, total symptom score increased significantly during both experiments in FD patients but not in controls. Throughout the experiments, total symptom score did not differ significantly in FD patients between the somatostatin experiment and placebo. With respect to individual symptoms such as nausea, postprandial fullness and epigastric tension, similar results were obtained.

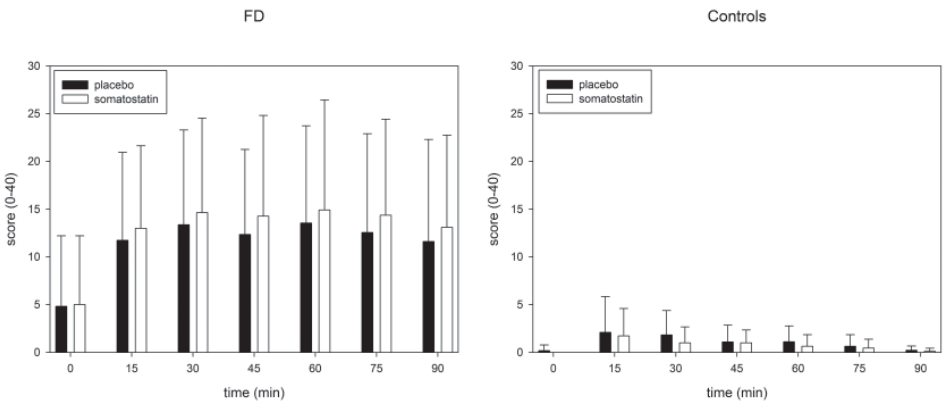

Figure 7.5. Total symptom scores before and after meal ingestion in FD and controls in response to somatostatin and placebo.

Discussion

Magnetic Resonance Imaging is a non-invasive technique that allows simultaneous measurement of several gastric functions, such as gastric emptying, volume changes, and motility (contractions).

The observed reductions in total gastric volume by somatostatin resulted from changes in gastric content and not from changes in intragastric air. Gastric emptying of the liquid meal was significantly accelerated during somatostatin infusion both in healthy volunteers and FD patients. Published data on gastric emptying in response to somatostatin or octreotide are not in line (7-12). Van der Ohe et al. (11) observed an acceleration of initial gastric emptying of solids in response to 50 mcg octreotide subcutaneously. In contrast, Maes et al. (9) using

a similar dose, observed a marked delay in gastric emptying of solids in healthy volunteers using an isotope breath test. Okamoto et al. (8) observed a delay in gastric emptying of liquids using a dose of 50 mcg octreotide subcutaneously. Foxx-Orenstein et al. (10) studied the effect of different doses of octreotide (30 and 100 mcg subcutaneously) on liquid and solid gastric emptying using radionuclide scintigraphy. In that study, octreotide delayed gastric emptying of solids but not of liquids. Using a similar dose of octreotide, Van Berge Henegouwen et al. (12) observed an acceleration of gastric emptying of a liquid meal. Differences in results between the various studies may be related to the technique employed to measure gastric emptying, to the doses of octreotide or somatostatin and also to meal composition and meal consistency. Therefore the results of the various studies cannot be directly compared. An advantage of MRI over other techniques is that not only emptying but also volume changes and contractions can be measured simultaneously and can be related. When analyzing the previous studies (8,11) in more detail it is obvious that somatostatin accelerates the early phase of gastric emptying but delays the late phase of gastric emptying. In our protocol, we measured gastric emptying up to 90 min and therefore late emptying data are not available. The acceleration in gastric emptying by somatostatin might result from several factors. First, the lag phase was significantly shorter pointing to more readily onset of gastric emptying. Second, during somatostatin a significantly higher emptying rate was observed. Third, gastric postprandial contraction frequency was not affected by somatostatin but the contraction pattern changed during somatostatin infusion and became more regular. Pyloric tone is also known to affect emptying rate. Little is known however on the response of the pylorus to somatostatin or octreotide (24). Previous studies have shown an inhibitory effect of somatostatin on secretion of gastrin (25) and gastric acid, thereby affecting the volume of gastric contents.

Contractions in the antrum or more distal part of the stomach typically occur at a maximum frequency of about 3 per min. We did not observe any differences in contraction frequency between experiments, suggesting that somatostatin does not influence gastric motility. Although somatostatin has been shown to inhibit antral contractions in the fasting state, results concerning the effect of somatostatin on postprandial antral motility are not in harmony (8,26,27). Our results are in line with a previous study by Okamoto et al. (8) using ultrasound. These authors did not observe a difference in postprandial contraction frequency between octreotide and

placebo, but contraction amplitude and motility index was significantly affected during the octreotide experiment (8).
An inhibitory effect of octreotide and somatostatin on visceral perception in healthy subjects has been reported previously (13,15), but controlled data on the effect of somatostatin or octreotide on visceral perception or dyspeptic symptoms in FD are lacking. The FD patients with postprandial symptoms we studied had a gastric half emptying time that was significantly delayed compared to controls. Although somatostatin significantly accelerated gastric emptying in the FD patients, no effect on postprandial symptoms such as nausea, fullness or epigastric tension was observed. Postprandial symptoms in FD patients may result from various factors or mechanisms. Impaired gastric accommodation may account for up to 40% of dyspeptic symptoms as indicated by Tack et al. using a barostat (28). We have not measured gastric accommodation, only gastric volumes. The more rapid gastric emptying induced by somatostatin may reduce symptoms of delayed emptying but on the other hand, may provoke symptoms due to more rapid delivery of nutrients to the duodenum. Enhanced perception in response to intraduodenal infusion of nutrients and acid has been shown in FD (29,30). In previous studies, a positive correlation between somatostatin levels and the degree of symptoms in FD patients has been documented (31,32).
We conclude that, measured with MRI, somatostatin reduces postprandial gastric volumes in both health and disease (FD), through earlier initiation and acceleration of gastric emptying without quantitatively affecting gastric motility. Somatostatin did not result in postprandial symptom reduction in FD patients.

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