MRI for evaluation of gastric physiology

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Chapter 6

Effect of somatostatin on gastric function measured with magnetic resonance imaging

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Abstract

Delayed gastric emptying and impaired gastric accommodation have been identified as possible pathophysiological mechanisms in Functional Dyspepsia (FD). Somatostatin has several effects on the gastrointestinal tract. Data on the effect of somatostatin on gastric emptying are conflicting and data on the effect of somatostatin on gastric accommodation is limited.

Objectives

To explore in a mechanistic study the effect of somatostatin on gastric emptying, gastric accommodation and motility in health and FD using Magnetic Resonance Imaging (MRI).

Methods

Eleven healthy subjects (controls) and eleven patients with FD participated in a randomized, placebo-controlled study. The effect of either saline or somatostatin on gastric function in response to a meal was studied on separate days using three-dimensional volume scans and two-dimensional dynamic scans.

Results

Stomach volume was significantly smaller throughout the somatostatin experiment in both patients and controls; mean difference of 70 (24) ml and 109 (12) ml respectively. Impaired accommodation was present in 18% of patients and 40% of controls had impaired accommodation in response to somatostatin.
Gastric contents were significantly smaller throughout the somatostatin experiment compared to placebo in both patients and controls; mean difference of 80 (10) ml and 77 (12) ml respectively.

Conclusions

We have shown that the MRI technique allows non-invasive measurement of gastric accommodation in health and disease and in response to a pharmaceutical

intervention. Furthermore, we have shown that somatostatin impairs gastric accommodation and accelerates gastric emptying in controls. In FD, somatostatin accelerates gastric emptying and does not reduce postprandial symptoms.

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 in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms. Symptoms may consist of postprandial fullness, early satiation, or epigastric pain/ burning (1).

Several pathopysiological mechanisms have been identified in FD, including delayed gastric emptying, abnormal antroduodenal motility, visceral hypersensitivity and impaired gastric accommodation (2). Previous studies employing the barostat technique have provided evidence for visceral hypersensitivity and impaired gastric accommodation in subsets of FD patients (3-5).

Somatostatin is a cyclic tetradecapeptide distributed throughout the nervous system and gastrointestinal tract (6). Somatostatin and its long acting synthetic analogue octreotide are well known for its inhibitory effects on gastric acid and pancreatic secretion, gallbladder and small bowel motility (7). Results on the effect of somatostatin and octreotide on gastric emptying, however, have been conflicting (8-12). While several authors found an accelerating effect (11,12) on gastric emptying, others found evidence for an inhibitory effect (8-10).

Both somatostatin and octreotide reduce visceroperception in the upper gastrointestinal tract and therefore have potential in the treatment of dyspeptic symptoms (13,14). Data on the effect of either somatostatin or octreotide on gastric accommodation is limited. Mertz et al. (15) have shown 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. Controlled data on the effect of either somatostatin or octreotide on gastric accommodation and visceral perception in FD patients is lacking.

In recent years, Magnetic Resonance Imaging (MRI) has become available as a noninvasive alternative technique to study gastric emptying, accommodation and

motility simultaneously (16-19). Aim of our study was to explore in a mechanistic study the effect of somatostatin on gastric emptying, gastric accommodation and motility in health and FD using MRI.

Materials and methods

Subjects

Eleven patients with FD (four men, seven women; mean age 44 years; range 28-62 years; BMI 24.4 ± 3.3 kg/m2) and eleven healthy subjects (six men, five women; mean age 25 years; range 19-51 years; BMI 22.4 ± 3.0 kg/m2) participated in the study. Patients were selected from the outpatient clinic and fulfilled criteria for FD. 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 the Leiden University Medical Center (LUMC) 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 saline or somatostatin (Somatostatin UCB, UCB Pharma BV, Breda, The Netherlands). Infusion of saline or somatostatin (250 µg/h) 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 (30º) and remained within the MRI scanner throughout the experiment.
The experiment started with a three-dimensional (3D) volume scan and a two-dimensional (2D) 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 (up to 400 ml) was provided. 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). After completion of the final measurement (t=90 min) the subject was removed from the MRI scanner.

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) Fasting stomach volume (ml) was defined as the volume in the period prior to consumption of the meal. 2) Postprandial stomach volume was defined as the mean of the volumes acquired at 15 and 30 min. postprandial. 3) Accommodation volume was defined

as the difference between postprandial and fasting stomach volumes (22). Gastric motility parameters were obtained at 10 equally distributed points perpendicular to the stomach axis. Peristaltic contractions (Fig. 6.1) were detected and their frequency per minute was calculated (17,21).

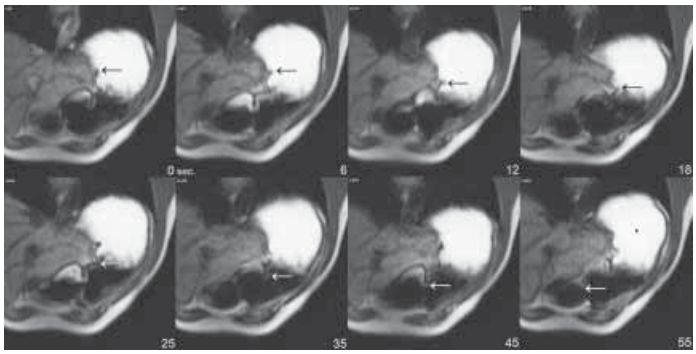


Figure 6.1. Dynamic scan sequence showing peristaltic contractions in the stomach. Peristaltic contractions (arrow) are running from the fundus to the antrum. The gadolineum labelled meal is clearly visible.

Statistical analysis

Data was analyzed using a statistical software package (SPSS® for Windows Release 14.0, 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

Fasting stomach volumes

Fasting stomach volumes at t=0 min did neither differ significantly FD patients and controls (healthy subjects) nor between somatostatin and placebo within controls and FD patients (Table 6.1).

	FD		Controls	
	somatostatin	placebo	somatostatin	placebo
Fasting stomach volume (ml)	78 ± 67	59 ± 52	56 ± 27	68 ± 23
Postprandial stomach volume (ml)	484 ± 105	507 ± 92	465 ± 56*	530 ± 42
Accommodation volume (ml)	412 ± 58	450 ± 87	409 ± 58*	462 ± 43

*Table 6.1. Stomach volumes (ml) measured with MRI in response to a liquid meal. Fasting stomach volume (FSV) represents the stomach volume prior to meal ingestion. Postprandial stomach volume (PSV) represents the mean stomach volume over the first 30 min. postprandial. Accommodation volume is defined as PSV minus FSV. Data are shown as mean ± SD. *p<0.05 compared to placebo.*

Postprandial stomach volumes

Stomach volume increased significantly in FD patients immediately after meal ingestion to 502 ± 99 ml and 495 ± 93 ml for somatostatin and placebo respectively. A similar increase in stomach volume was observed in controls, where stomach volume increased to 500 ± 67 ml and 523 ± 44 ml for somatostatin and placebo, respectively.

Throughout the experiment stomach volume was 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). Moreover the area under the curve for stomach volume was significantly smaller for the somatostatin experiment compared to placebo in both FD patients (36261 ± 11944 ml·min vs. 41773 ± 9707 ml·min) and controls (31833 ± 6243 ml·min vs. 40818 ± 3667 ml·min).

Table 6.1 shows fasting and postprandial stomach volumes for both experiments. Accommodation volume in response to a meal was 462 ± 43 ml for controls. The lower range of normal (mean-2SD) for the accommodation volume was 376 ml (Fig. 6.2a). During somatostatin infusion, accommodation volume in response to a meal was impaired in 3 out of 11 (27%) controls (Fig. 6.2a). Moreover, accommodation volume in response to a meal was significantly smaller for the somatostatin experiment compared to placebo in controls; 409 ± 58 vs. 462 ± 43, respectively. Two patients with FD (18%) had an impaired accommodation volume

when using the lower range of normal as a cutoff (Fig. 6.2b). During somatostatin infusion, accommodation in response to a meal was impaired in 4 out of 10 (40%) patients with FD when using the lower range of normal as a cutoff (Fig. 6.2b)

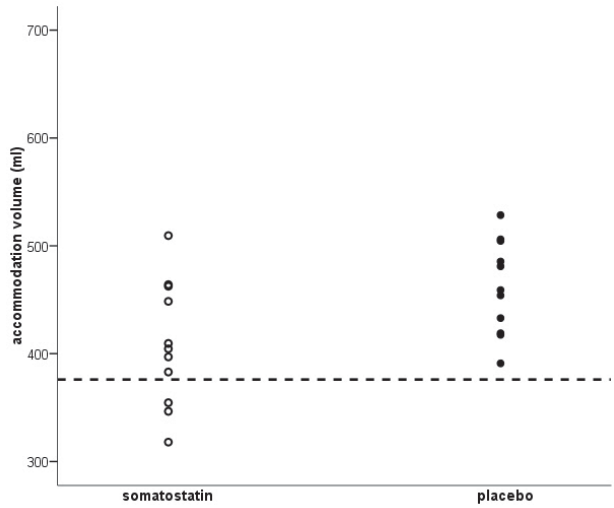


Figure 6.2a. Accommodation volume (ml) in response to a liquid meal in 11 healthy subjects. Under somatostatin three out of 11 subjects (27%) show an impaired accommodation volume (< 376 ml).

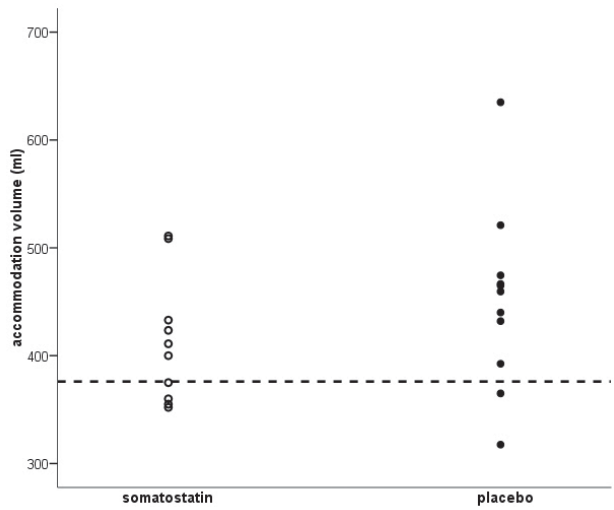


Figure 6.2b. Accommodation volume (ml) in response to a liquid meal in 11 patients with FD. Two out of 11 (18%) patients show an impaired accommodation volume (< 376 ml) under placebo. Under somatostatin four out of 10 patients (40%) show an impaired accommodation volume (< 376 ml).

Gastric contents

Figure 6.3 shows the influence of somatostatin on gastric contents during the digestive period in FD patients and controls. Immediately after meal ingestion at t=15 min gastric contents increased significantly to 382 ± 44 ml and 399 ± 53 ml for somatostatin and placebo respectively in FD patients. A similar increase in gastric contents was observed in controls; gastric contents increased to 389 ± 43 ml and 407 ± 41ml for the somatostatin and placebo experiment, respectively.

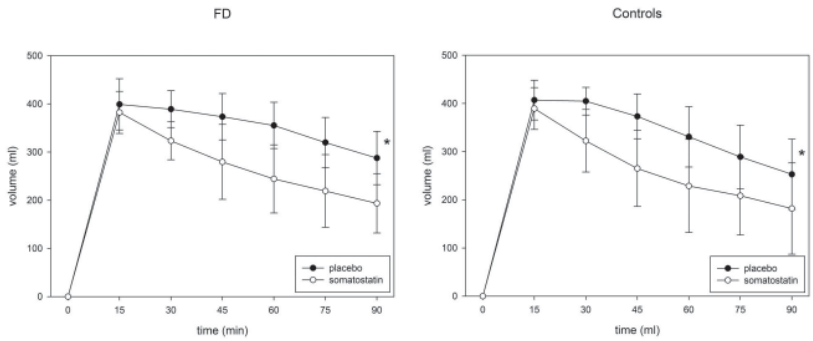


Figure 6.3*. Gastric contents (ml) before and after meal ingestion in FD and controls in response to somatostatin and placebo. Values are shown as mean ± SD. * p<0.05 compared to somatostatin throughout the experiment.*

Throughout the experiments gastric contents were significantly smaller for the somatostatin experiment compared to placebo in both FD patients (mean difference 80 (10) ml) and controls (mean difference 77 (12) ml). Moreover the area under the curve for gastric contents was significantly smaller for the somatostatin experiment compared to placebo in both FD patients (23178 ± 4405 ml·min vs. 29701 ± 3647 ml·min) and controls (22569 ± 5619 ml·min vs. 28960 ± 3639 ml·min).

Intragastric air

At the start of the digestive period, t=0 min, intragastric air volume did not differ significantly between the experiments in FD patients and controls (Fig. 6.4). After meal ingestion air volume increased significantly in FD patients and controls. Throughout the experiments air volume increased slightly in FD patients and controls (Fig. 6.4). In controls, but not in FD patients, air volume was significantly smaller throughout the somatostatin experiment compared to placebo; mean difference of 31 (9) ml.

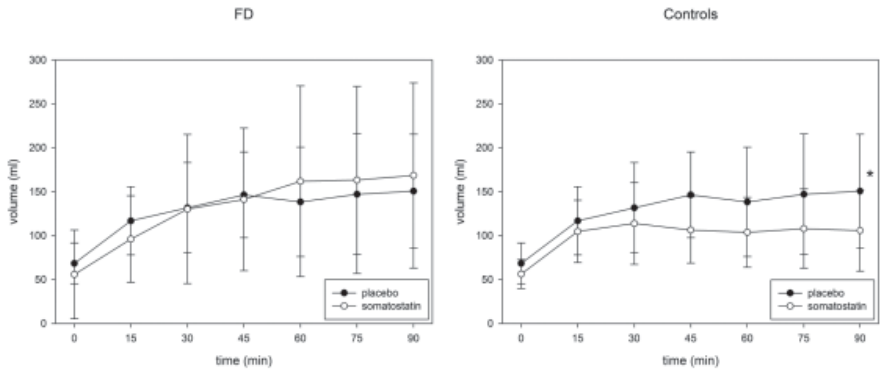


*Figure 6.4. Intragastric air (ml) before and after meal ingestion in FD and controls in response to somatostatin and placebo. Values are shown as mean ± SD. * p<0.05 compared to somatostatin throughout the experiment.*

Gastric motility

Gastric contractions are visualized in Figure 6.5. The contraction frequency did not differ significantly between the experiments neither in FD patients nor in controls (Table 6.2).

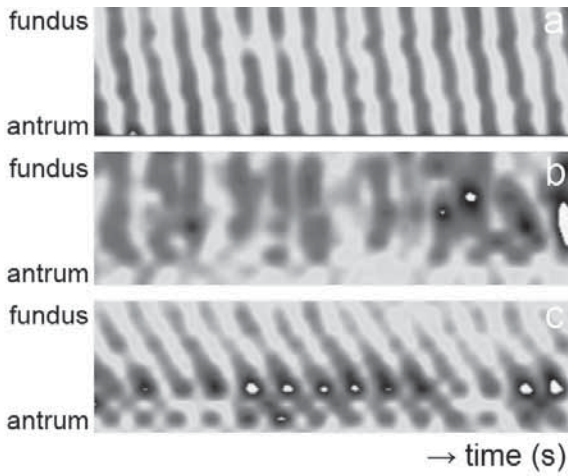


Figure 6.5. Visualization of contraction patterns show a 5 min. period prior to meal ingestion (a) and after meal ingestion during placebo infusion (b) and somatostatin infusion (c). The x-axis shows time and the y-axis shows the location in the stomach from fundus to antrum. Color gradients represent gastric occlusion (darker is more occluded). In this example the irregular postprandial pattern during placebo infusion was "restored" to a more regular pattern during somatostatin infusion.

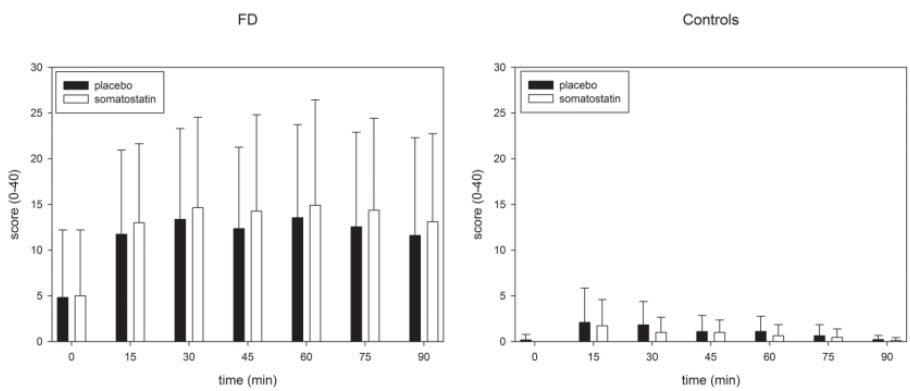
	0	15	30	45	60	75	90 (min)
Controls							
somatostatin	14.4±1.4	13.4±1.6	14.9±1.0	14.8±1.3	14.6±0.9	14.1±0.9	13.9±0.8
placebo	14.1±1.0	13.8±1.7	14.2±1.3	14.5±0.9	14.3±0.8	14.5±0.9	14.6±1.2
FD							
somatostatin	14.8±2.1	13.3±2.2	15.4±1.9	14.6±1.4	15.1±1.3	14.1±2.3	15.1±1.2
placebo	15.0±1.4	12.3±2.3	14.5±2.0	15.3±1.3	15.1±1.3	14.4±2.1	14.9±1.5

Values are mean ± SD.
Table 6.2. Effect of somatostatin on gastric contractions (contactions per 5 min) in controls and FD.

The analysis method does not allow us to further quantify other motility parameters. However, we are able to visualize the contraction pattern in a similar manner as Marciani et al. (19) did previously.

Dyspeptic symptoms

Total symptom score (range 0-40) prior to meal ingestion was significantly higher in FD patients compared to controls for both experiments (Fig. 6.6). After meal ingestion total symptom score increased significantly in FD patients during both experiments, in contrast to controls. Throughout the experiments total symptom score did not differ significantly in FD patients.



Values are shown as mean ± SD.
Figure 6.6. Total symptom scores (mean ± SD) before and after meal ingestion in FD and controls in response to somatostatin and placebo.

Similar results were observed for the individual symptoms: nausea, postprandial fullness and epigastric tension. However, in FD patients epigastric discomfort/pain was significantly higher throughout the somatostatin experiment compared to placebo; 2.9 (0.3) vs. 1.9 (0.3), respectively.

Discussion

We have provided data on the effect of a pharmacological intervention on several gastric functions (accommodation, emptying, volume changes and contractions) measured simultaneously with a single technique, Magnetic Resonance Imaging. We have shown that somatostatin affects gastric accommodation in response to a meal in both health and disease (FD patients). We confirm previous observations (10,15) in healthy subjects that somatostatin reduces postprandial gastric accommodation and are the first to report on the effect of somatostatin on gastric accommodation in FD patients. Further evidence is provided that with the non-invasive MRI technique one is capable to measure changes in accommodation as a volume response. Not only did we observe that 18% of patients with FD had impaired accommodation, we also observed a substantial decrease in gastric accommodation during somatostatin infusion in health. During somatostatin infusion 27% of healthy subjects and 40% of FD patients had impaired accommodation. We are well aware that the observed percentage of FD patients who had impaired accommodation (18%) is substantially lower than the number (40%) observed by Tack et al. (5) Moreover, we did not observe a significant difference in accommodation volume between patients with FD and controls. The reason for this discrepancy in results is not apparent but several factors may be involved. First, we have measured the accommodation response with the non-invasive MRI instead of the invasive barostat technique. Second, during barostat recording intragastric bag pressure is set at a pressure above abdominal pressure, in order to allow optimal contact between barostat bag and stomach wall. Third, the barostat bag is located for most part in the proximal stomach while the MRI volume data covers total intragastric volumes. Fourth, we have recently shown during simultaneous barostat and MRI recording that gastric accommodation as measured by MRI with the inflated barostat bag in situ was less pronounced or not observed in the absence of the barostat bag. Therefore accommodation

data based on barostat recordings should be re-evaluated with respect to their physiological significance. Further MRI studies, as the present one, that evaluate the accommodation response in health and disease are required to better understand gastric (patho)physiology. Moreover, the number of FD patients we studied is small and limits our conclusions concerning the presence of impaired accommodation detected with the MRI technique in FD.

We have shown that gastric emptying of a liquid meal was increased during somatostatin infusion in both health and FD. These data are in line with previous studies showing enhanced gastric emptying in response to somatostatin or its long-acting analog octreotide in health (7,11,12). Published data on gastric emptying in response to somatostatin or octreotide have been conflicting. Van der Ohe et al. (11) observed an acceleration of initial solid gastric emptying in response to 50 mcg octreotide subcutaneously. In contrast, Maes et al. (9) using a similar dose observed a marked delay in solid gastric emptying in healthy volunteers using 14/13C breath test and Okamoto et al. (8) observed a delay in liquid gastric emptying 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 radionuclear scintigraphy. In their study octreotide delayed solid gastric emptying, but did not affect liquid gastric emptying. Using a similar dose of octreotide Van Berge Henegouwen et al. (12) observed an acceleration of gastric emptying of a liquid meal. As the various studies differ with respect to doses, meal composition and the technique applied to measure gastric emptying, differences in the results may be the consequence of methodological differences.

We studied gastric emptying for 90 min showing an increase in gastric emptying. Previous studies (8,11) have shown that somatostatin increases early gastric emptying but decreases late gastric emptying. Due to the length of our study late gastric emptying could not be analyzed, hence a late change in gastric emptying could have been missed. When analyzing our data in more detail, it is obvious that the difference in gastric emptying induced by somatostatin was not due to a difference in emptying rate between somatostatin and placebo. We already observed a difference in gastric emptying during the somatostatin experiment immediately after meal intake. This difference might result from several factors. First, it might be due to a shorter duration of the lag phase. Volume changes after meal intake were more pronounced during somatostatin infusion compared to placebo in both FD patients and controls, pointing to a shorter lag phase and more ready onset of gastric emptying. Second, gastric contractions may

have been affected by somatostatin; however, we did not observe a difference in gastric contraction frequency. Third, pyloric tone may have been influenced by somatostatin explaining the shorter lag phase. Little is known on the response of the pylorus to somatostatin or octreotide (23). Fourth, previous studies in animals have shown an inhibitory effect of somatostatin on gastrin release by the antral G cells (24), thus reducing gastric acid secretion and most likely also the volume of gastric contents. Interestingly we did not find a difference in contraction frequency in our study, 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 conflicting (8,25,26). Our results are in line with a previous study by Okamoto et al. (8) who studied the effect of octreotide on postprandial gastric motility in healthy subjects using ultrasound. These authors did not observe a difference in contraction frequency between octreotide and placebo, neither after a liquid nor after a solid meal. They did however observe a significant reduction in contraction amplitude and motility index during the octreotide experiment (8).

The effects of octreotide and somatostatin on visceral perception in healthy subjects have been reported previously (13,15), but data on the effect of somatostatin or octreotide on visceral perception in FD were lacking. In our study somatostatin did not reduce postprandial symptoms, such as nausea, fullness and epigastric tension in FD patients. These data correspond with the observation that somatostatin does not improve gastric accommodation in FD. Impaired gastric accommodation is considered an important pathophysiological mechanism in the occurrence of symptoms like postprandial fullness and early satiety in FD (27). Pharmacological interventions that result in gastric relaxation are considered to have therapeutic potential in FD. Furthermore, we observed an increase in epigastric pain/discomfort in response to somatostatin. An enhanced perception in response to intraduodenal infusion of nutrients and acid has also been shown in FD (28,29). Our observation that somatostatin accelerates gastric emptying might explain this increase in visceroperception, as accelerated gastric emptying increases the intraduodenal load of nutrients. In previous studies a positive correlation between somatostatin levels and the degree of symptoms in FD patients has been documented (30,31).

We have shown that the MRI technique allows us to non-invasively measure and calculate gastric accommodation in health and disease and in response to a pharmaceutical intervention. Furthermore, we have shown that: 1) Somatostatin

impairs gastric accommodation, but the effect is significant only in controls and not in FD patients. 2) Somatostatin accelerates gastric emptying in both controls and FD patients. 3) Somatostatin does not result in postprandial symptom reduction in FD patients. 4) Somatostatin does not affect postprandial gastric motility as shown by contraction frequency.

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