Impaired drinking capacity in patients with functional dyspepsia: intragastric distribution and distal stomach volume

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Abstract The water drink test is a good tool to evoke dyspeptic symptoms. To what extent these symptoms are related to altered gastric distribution is not clear. Therefore, we determined gastric volumes after a drink test using SPECT. After a baseline scan 20 healthy volunteers (HV) and 18 patients with functional dyspepsia (FD) underwent a drink test (100 mL min\(^{-1}\)) followed by five scans up to 2 h. Dyspeptic symptoms were scored before every scan. A Wilcoxon signed rank test (P < 0.05) and a mixed effects model were used for statistical analyses. Fasting volumes were significantly higher in FD compared to HV for total, proximal and distal stomach (P < 0.001). Functional dyspeptic patients ingested significantly less water (P < 0.001) and had an impaired filling of the distal part of the stomach (P = 0.001) after the drink test. In FD, bloating (prox. 80%, dist. 56%), pain (prox. 87%, dist. 62%) and fullness (prox. 80%, dist. 59%) were determined more by proximal stomach volume rather than distal stomach volume. These data suggest that drinking capacity is mainly determined by antral volume, with a reduced antral filling in FD compared to HV. The persisting symptoms of bloating, pain and fullness in FD are predominantly associated with proximal stomach volume.

Keywords drink test, functional dyspepsia, intragastric distribution, single photon emission computed tomography.

Abbreviations SPECT, single photon emission computed tomography; FD, functional dyspepsia; VAS, visual analogue scale.

INTRODUCTION

Functional dyspepsia [FD] is a prevalent disorder characterized by upper abdominal discomfort or pain not explained by structural or biochemical abnormalities. Several pathophysiological mechanisms, including impaired meal-induced relaxation and visceral hypersensitivity to distension of the proximal stomach have been suggested to explain the presence of dyspeptic symptoms such as bloating, nausea, early satiety, fullness and weight loss. Some studies have associated both early satiety and weight loss with impaired meal-induced accommodation, whilst others associated fullness with antral distension. However, subdividing the FD patient groups based on their predominant symptoms has not reliably led to the identification of the underlying pathophysiological mechanism.

The drink test has been proven to be a useful non-invasive diagnostic tool to study FD in a more physiological setting. Several studies have revealed that FD patients exhibit a reduced drinking capacity during a water or caloric drink test and that the dyspeptic symptoms evoked by the drink test persist longer in FD patients compared to healthy volunteers (HV). These findings are in line with reports that patients with FD often relate the onset or aggravation of their symptoms to meal intake. However, the underlying mechanisms leading to these observed differences in drinking capacity between FD patients and HV are not known. Previously, we could not establish a prominent relationship between gastric hypersensitivity to balloon distension or impaired accommodation and
the outcome of the drink test. In other words, although there is strong evidence indicating that dyspeptic symptoms correlate with impaired meal-induced relaxation and visceral hypersensitivity, our drink test failed to predict the presence of these abnormalities in proximal stomach function. Conversely, these data suggest that the impaired drinking capacity of FD patients cannot be explained by altered proximal stomach function. An alternative explanation could be that the drinking capacity is rather determined by antral distension. We hypothesize that the antrum is becoming overloaded by the ingested amount of water during the drink test, especially, as several studies suggest a possible role for the antrum in the development of dyspeptic symptoms.

Single photon emission computed tomography (SPECT) based Gastric Volume Scintigraphy is a non-invasive tool based on i.v. injected radiolabelled technetium-99m (99mTc)-pertechnetate.18 This marker accumulates in the gastric mucosa, thereby allowing 3-dimensional imaging of the stomach in both the fasting and postprandial states. Single photon emission computed tomography has been validated and has been used to evaluate drug and meal induced changes in the gastric volume in several pharmacological studies. In the present study, we applied this technique to determine the relationship between the maximal ingested volume, the intragastric distribution and symptoms after the water drink test in both HV and FD patients.

MATERIALS AND METHODS

Subjects

Healthy subjects with no previous abdominal surgery and taking no medication were recruited by public advertisement. These subjects were invited to participate if the Nepean Dyspepsia Index (NDI) score did not exceed 5, a cut-off used in previous studies. The NDI is a validated disease specific index that scores frequency [0–4], severity [0–5] and discomfort [0–4] of 15 dyspeptic symptoms with a maximal score of 195.24 In addition, patients from the outpatient clinic or patients referred to the endoscopy unit for upper endoscopy with an NDI score above 25, were included consecutively if they fulfilled the Rome II criterion for FD and if endoscopy was negative, i.e. no organic abnormality possibly explaining the dyspeptic complaints was encountered during the endoscopy. Patients on acid-suppressive drugs had to stop medication at least 5 days before the study. Drugs known to affect gastrointestinal motility were discontinued at least 48 h before the study. All the subjects gave written informed consent before the study. The study protocol was approved by the Medical Ethical Committee of the Academic Medical Centre, Amsterdam, The Netherlands.

Experimental protocol

After an overnight fast and 30 min after intravenous injection of 200 MBq 99mTc-pertechnetate a baseline scan was performed to measure the fasting gastric volumes. Once the baseline scan was completed, the subjects were invited to undergo a water drink test. The subjects were asked to drink water at a rate of 100 mL min−1. When the subject reached maximal intake, the end-point of the drink test, the number of beakers emptied x 100 mL was recorded as the maximal ingested volume. Directly after the drink test was completed another scan was made followed by scans every 30 min up to 2 h. Before every scan was made symptoms of epigastric bloating, nausea, pain, satiety, fullness, hunger and epigastric burning were recorded on a visual analogue scale (VAS) from 0 to 100 mm (ranging from 0 = ‘no sensation’ and 100 = ‘very severe discomfort’).

SPECT imaging

Gastric imaging was assessed by means of SPECT scanning. Intravenous injection of 99mTc sodium pertechnetate, which is taken up by the parietal and non-parietal cells of the gastric mucosa, allows visualization of the stomach wall with SPECT scanning. To limit radiation exposure, a dose of 200 MBq 99mTc-pertechnetate was administered, limiting the radiation burden to 2.4 mSv. We have determined that this dose is capable of delivering good quality images for at least 2.5 h after i.v. injection. The total radiation exposure was within permissible ranges for research and clinical studies. This study was approved by the radiation board of the Academic Medical Centre, Amsterdam, The Netherlands. Tomographic images of the gastric wall were obtained by using a dual head gamma camera in SPECT mode (GE Varicam, Haifa, Israel) enabling a 3 dimensional data acquisition. Any background interference from the small intestine, the heart or the kidney was carefully removed before analysis to prevent errors in volume calculations. After reconstruction, stomach volume measurements were performed using the volume tool software on the Hermes processing station. A threshold of 20% of the maximal voxel count value was applied, after filling the interior stomach with a default 50% voxel count value.

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Data analysis

SPECT The time required to obtain a 360 degree scan of the stomach takes 7 min. Therefore, baseline (fasting) and postdrink test volumes were measured as the volume of 7-min periods using the volume tool software on the Hermes processing station (Hermes, Nuclear Diagnostics, Stockholm, Sweden). Total and regional (proximal–distal) gastric volumes were calculated. The stomach was divided into proximal and distal stomach by drawing a horizontal line across the incisura,19,18 an anatomical landmark visualized by SPECT scanning. Total, proximal and distal stomach volumes were expressed as absolute volumes (mL) and volumes relative to baseline (Δ mL). To evaluate the distribution of gastric volumes over the proximal and distal stomach, the proximal/distal stomach ratio was calculated. For all results, the fifth and 95th percentile were considered the lower and upper limit of the normal range based on the HV data. In addition, correlations were calculated to evaluate to what extent the increase in gastric volume correlated to the amount of the ingested water.

Symptoms Symptoms reported before and after the drink test are expressed individually for every scan period. Individual sensation scores for bloating, nausea, pain, satiety, fullness, hunger and burning were assessed on a VAS, from which an individual score and a total symptom score for each time point were calculated.

Statistics The data on the groups are expressed as mean values ± standard error of the mean (SEM). The data from the HV and the patients with FD were compared using a Mann–Whitney U-test. Any difference was considered significant if the P-value was <0.05. A mixed effects model was used to examine the relationship between variations in symptoms and gastric volumes. To allow for variation between participants, individual constants and slopes (random effects) were obtained. This model is used to estimate to what extent the change in symptoms can be explained by the change in postdrink test gastric volumes.

RESULTS

Subjects All subjects completed the study and did not experience adverse events. Twenty HV [13 women, seven men, mean age, 24 [19–52] years] and 18 patients with FD [five women, 13 men; age 39 [23–65] years] were included in the study. Healthy volunteers had an NDI score of 0 ± 0.3, whereas FD patients had a NDI score of 73.9 ± 8.7 (P < 0.001). There was a significant difference in age [39 [23–65] years vs 24 [19–52] years; P < 0.001], body mass index [25.2 ± 1.2 vs 22.3 ± 0.8 kg m⁻²; P = 0.041] and weight [78 ± 4.5 vs 68 ± 3.1 kg; P = 0.044 respectively] between FD and HV. Gender distribution was not significantly different between the two groups (chi-squared test), although a type-II error could have occurred. The predominant NDI symptoms (frequency 9 days or more in 14 days) in FD patients were bloating [72%], fullness [72%] and pain [61%], whereas symptoms of early satiety occurred in 28% of the FD patients. The severity of the NDI symptoms [scored severe to very severe] was 45% for pain, 46% for bloating, 38% for fullness and 20% for early satiety.

Fasting conditions

SPECT scanning In HV, the fasting volumes of total, proximal and distal stomach were 225 ± 18, 184 ± 12 and 41 ± 8 mL respectively [Fig. 1]. The 95th percentile of total, proximal and distal stomach volume revealed cut-off values of 332, 261 and 73 mL respectively. The proximal/distal stomach ratio was 5.56 ± 0.42 for HV, with 2.66 as the fifth percentile cut-off.

In FD patients, the fasting total, proximal and distal gastric volume was significantly larger compared to HV [351 ± 18 mL; P < 0.001, 264 ± 9 mL; P < 0.001 and 87 ± 12 mL; P < 0.001 respectively] [Fig. 1]. When using the 95th percentile of normal values as upper limit, fasting total, proximal and distal stomach volume were abnormal in 61%, 44% and 61% of the FD patients respectively. In addition, the proximal/distal stomach ratio was significantly lower in FD patients [4.19 ± 0.61; P = 0.01] compared to HV. Using the fifth percentile of fasting proximal/distal stomach volume ratio for HV as the lower limit, 39% of the FD patients had an abnormal low proximal/distal stomach volume ratio, illustrating that in these FD patients, the distal stomach volume contributes relatively more to the total gastric volume than in HV.

Relationship between clinical symptoms (NDI) and volumes Functional dyspepsia patients with an increased fasting total stomach volume [≥95th percentile of HV] reported significantly more bloating on the NDI compared to patients with normal total stomach volumes [9.3 ± 1.1 vs 6.9 ± 0.7; P = 0.027]. Patients with an abnormally low fasting proximal/distal
stomach ratio (≤5th percentile of HV) scored significantly more severe bloating on the NDI compared to patients with normal proximal/distal stomach volume ratios (3.6 ± 0.2 vs 2.4 ± 0.4; \(P = 0.044\)). Other clinical symptoms were not significantly more present in any subgroup.

**DRINKTEST**

Maximal ingested volume and intragastric distribution

**Drinking capacity** Healthy volunteers drank on average 1818 ± 153 mL of water leading to a significant increase in the total, proximal and distal gastric volumes. The lower limit of the ingested amount of water was defined by the fifth percentile [1100 mL]. Compared to HV, FD patients drank significantly less water (1148 ± 143 mL; \(P < 0.001\)). Using the fifth percentile as cut-off, 50% of the FD patients had an abnormal low water intake.

**SPECT scanning: intragastric distribution at maximal ingested volume** The absolute total stomach volume directly after the drink test (Fig. 2) was significantly lower in FD compared to HV (1851 ± 137 mL vs 2405 ± 158 mL; \(P = 0.020\)). Whilst proximal stomach filling was not significantly different between FD and HV [1531 ± 116 mL vs 1801 ± 122 mL; \(P = 0.14\)], filling of the distal stomach was significantly reduced in FD compared to HV [321 ± 35 mL vs 605 ± 49 mL; \(P < 0.001\)]. This reduced antral filling is reflected in a significantly higher proximal/distal stomach volume ratio directly after the drink test in FD patients (6.4 ± 1.3 vs 3.3 ± 0.4; \(P = 0.001\)) (Fig. 3).

To further evaluate the possible relationship between the ingested volume and the gastric volume assessed by SPECT scanning, we also measured the

![Figure 1](image1.png)

**Figure 1** Fasting gastric volumes for healthy volunteers (HV) and functional dyspepsia patients with the 95th percentile for HV as upper limit.

![Figure 2](image2.png)

**Figure 2** Volumes measured by Gastric Volume Scintigraphy of total, proximal and distal stomach volume over time. (*\(P < 0.05\), **\(P < 0.01\), ***\(P < 0.001\) Mann–Whitney \(U\)-test).
volume increase after the drink test by subtracting fasting volume from the absolute volume. As expected from the difference in the water intake, the increase in total, proximal and distal gastric volume was significantly less in FD compared to HV (Fig. 4A). As shown in Fig. 4B, there was a strong correlation between the increase in gastric volume assessed by SPECT scanning and the maximum ingested amount of water, especially in the proximal stomach (\( R = 0.67 \ P = 0.001 \) vs \( R = 0.41 \ P = 0.073 \) [HV] and \( R = 0.91 \ P < 0.001 \) vs \( R = 0.52 \ P = 0.026 \) [FD]) for proximal vs distal stomach respectively. The total gastric volume increase was correlated to the total amount of the ingested volume \( [R = 0.61 \ P = 0.004 \] [HV] and \( R = 0.88 \ P < 0.001 \] [FD]) confirming our previous findings that SPECT scanning measures ingested volume rather than gastric tone.25

Relationship between intragastric distribution, maximal ingested volume and clinical presentation (NDI) Functional dyspepsia patients with a reduced water intake during the drink test (≤5th percentile of HV) scored a higher frequency of early satiety (3.6 ± 0.2 vs 2.2 ± 0.4; \( P = 0.019 \)) on the NDI compared to patients within the normal range of the water intake. There was no significant relationship between abnormally low postdrink test gastric volumes (≤5th percentile of HV) or abnormally high postdrink test ratios (≥95th percentile of HV) and any one of the clinical symptoms evaluated by the NDI questionnaire.

Drink test induced symptoms and intragastric distribution

Intragastric distribution after the drink test After the initial volume increase by the drink test, gastric volumes declined slowly over time returning to baseline values at 90 min after the drink test for both HV and FD patients (Fig. 2). The proximal stomach volume declined to a similar extent in HV and FD patients. However, in contrast to the proximal stomach volume, distal stomach volumes declined more rapidly in HV compared to FD patients over time. Furthermore, the reduced antral filling in FD patients, observed directly after the drink test, persisted up to 90 min resulting in a significantly lower distal stomach volume at 0, 30 and 60 min after the drink test compared to HV (Fig. 2).

Symptoms evoked by the drink test Before the drink test, no significant difference in reported symptoms was observed between FD patients and HV. In both HV and FD patients, all symptoms increased after the drink test and declined over time (Fig. 5). Symptoms persisted longer in FD patients compared to HV, resulting in significantly higher VAS scores for bloating, nausea, pain and fullness but not for satiety at 120 min after the drink test compared to HV (Fig. 5).

There was no significant difference in postprandial symptoms reported directly after the drink test by FD
patients with normal, compared to abnormal, gastric volumes, ratios or ingested volumes.

Relationship between drink test induced symptoms and intragastric distribution

To explain the variation in symptoms by postdrink test gastric volumes, a mixed effects model with random effects for each FD or HV on each factor was used. The percentages of symptoms associated with postdrink test gastric volumes are shown in Table 1. In HV, proximal and distal stomach volume explained dyspeptic symptoms to a similar extent. However in FD, bloating, epigastric pain and fullness were associated with the proximal stomach volume rather than with the distal stomach volume. There was no significant difference in postprandial symptoms reported by FD patients with normal, compared to abnormal, gastric volumes, ratios or ingested volumes.

DISCUSSION

In the present study, we confirmed that FD patients have larger fasting volumes and an impaired drinking capacity compared to HV. Most importantly, we showed that at the end of the drink test, mainly the volume of the distal stomach was impaired in FD, suggesting an important role for the distal stomach in limiting the fluid intake. Finally, we provide evidence that after a non-caloric maximal volume challenge, the persisting symptoms of bloating, epigastric pain and fullness in FD are predominantly associated with the proximal stomach volume.

Meal ingestion is an important trigger for dyspeptic symptoms in a majority of the FD, which in severe cases may even lead to impaired caloric intake and significant weight loss. In line with this observation, we and others showed that the maximal volume of a liquid meal or water tolerated by FD is impaired in approximately 50% of the patients. Especially, as the proximal stomach serves as a reservoir, we previously examined the possible role of impaired accommodation and visceral hypersensitivity. However, no prominent relationship between proximal stomach dysfunction and the outcome of the drink test could be established. To obtain a more integrated understanding...

Table 1 The variation in symptoms explained by gastric volumes using a mixed effects model with random effects for each FD or HV on each factor

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FD, functional dyspepsia; HV, healthy volunteers.
view of the possible relationship between intragastric distribution and the maximal drinking capacity, we performed SPECT scanning of the entire stomach at the end of the drink test. As previously shown, FD drank significantly less compared to HV, resulting in a reduced gastric volume. More detailed analyses revealed that mainly distal stomach filling was impaired in FD, as evidenced by the proximal to distal stomach ratio. This suggests that the filling of the distal stomach may be an important determinant of drinking capacity, at least in a non-caloric drink test. Previously, Calderella et al.\textsuperscript{14} indeed provided evidence that FD are more sensitive to antral filling compared to HV. In this study, FD patients reached their threshold for discomfort at approximately 138 mL filling of a balloon in the distal stomach, whereas HV did not report discomfort up to the highest volume tested (400 mL).\textsuperscript{14} Similarly, we demonstrated that the distal stomach volume at the end of the drink test was significantly lower in FD \([321 \pm 35 \text{ mL}]\) compared to HV [605 ± 49 mL].

Our findings are in contrast to previous studies showing a more distal redistribution of a meal in FD patients.\textsuperscript{37–40} Recently, Piessevaux et al.\textsuperscript{16} illustrated a distal redistribution after a meal in 50% of the FD patients. Although the lack of caloric content in our study results in a different physiological response that could account for the observed difference other factors could be involved. In our study, the stomach was visualized at maximal filling, whereas Piessevaux et al.\textsuperscript{16} performed sequential imaging of the stomach after a standard meal. This profound difference in the degree of gastric filling most likely affects intragastric distribution. One may even hypothesize that initially the meal is indeed preferentially directed towards the distal stomach at submaximal filling, as a result of the impaired basal tone of the antrum [increased fasting volume]\textsuperscript{17,28,27} and impaired accommodation of the proximal stomach to the meal intake.\textsuperscript{12,3} As filling of the stomach however continues, as achieved in our drink test, other dynamics may come into play. As shown by Calderella et al.,\textsuperscript{14} the maximal antral filling is significantly limited in FD eventually leading to discomfort. To what extent the impaired distal stomach filling in FD results from increased sensitivity to distention or reduced compliance of the distal stomach could not be determined from our data.

In addition to impaired drinking capacity, dyspeptic symptoms after the drink test persist longer in FD compared to HV.\textsuperscript{12,31,32} Therefore, we investigated the relationship between individual dyspeptic symptoms and gastric volumes over time using a mixed effects model. This model explained the variation in dyspeptic symptoms to an equal extent by the variation in proximal and distal stomach volume in HV. In FD, however, proximal stomach volume was more powerful than the distal stomach volume in explaining the variation in epigastric pain, fullness and bloating after a non-caloric maximal volume challenge. The finding of a strong correlation between the proximal stomach volume and symptoms evoked by the drink test seems contradictory to our conclusion that antral filling is the main factor determining volume ingestion. It should be stressed however that the relationship between distal stomach volume and maximal ingested volume as previous discussed is completely different from the relation between postdrink test symptoms and the proximal stomach. The maximal ingested volume and postdrink test symptoms are two completely different parameters, and should not be confused. The relationship between postdrink test symptoms and the proximal stomach is in line with the reports presented by Piessevaux et al.,\textsuperscript{16} who showed that severe fullness was significantly associated with proximal retention. It should be emphasized, however, that this relationship was weak suggesting that other factors must be involved. In addition, 2 h after the drink test, dyspeptic symptoms remained in FD patients although the stomach was emptied, suggesting that the duodenum was involved in the maintenance of dyspeptic symptoms. Recently, Delgado-Aros et al.\textsuperscript{33} introduced the concept of early gastric emptying in FD patients. These authors established that early gastric emptying was associated with a lower volume ingested and increased postprandial symptoms possibly due to an increased volume load to the small intestine.\textsuperscript{33} These findings together with our new data underline the importance of a multi-factorial approach to FD.

In the fastened state, we observed larger gastric volumes in patients with FD compared to HV. These findings are in accordance with previous SPECT\textsuperscript{34,31,33} and ultrasound\textsuperscript{17,35} studies. Recently the relationship between fasting gastric volumes assessed by SPECT scanning, maximum caloric intake during the drink test and symptoms after standardized meal intake was evaluated. The authors illustrated an association with low fasting volumes, decreased caloric intake and post meal symptoms in FD.\textsuperscript{33} In our study, we did not find an association between either low or high fasting volumes and drinking capacity or post drink test symptoms. We did, however, find a relationship between increased gastric fasting volumes and bloating reported as a clinical symptom [NDI]. It should however be noted that in our study, scans, drink test and symptoms scores were all performed simultaneously, whilst Delgado-Aros et al.\textsuperscript{33} combined the results of
the individual physiological test performed on separate days. Furthermore, we evaluated clinical symptoms and symptoms after a maximal volume intake with water in contrast to the evaluation of symptoms after the ingestion of a standardized meal. These differences are likely to contribute to the discrepancy in the outcome between these two studies.

A few confounding factors could have contributed to the observed differences in volume and volume distribution between HV and FD patients. Our patient and HV groups were not entirely matched age and body weight matched. Although age has no effect on the drinking capacity, increased body weight has been associated with an increased maximal tolerated volume of a nutrient drink test. Since our patient group drank significantly less water despite their higher body weight, the differences in drinking capacity cannot be explained by the differences in body weight. In contrast to our previous study, the difference in postdrink test symptoms between HV and FD patients was relatively small. This could be explained by the lower NDI score (73.9 ± 8.7 vs 91.5 ± 5.5) and higher drinking capacity (1148 ± 143 vs 893 ± 70 mL) in the present study compared to our previous study, suggesting a milder form of FD in these patients. Especially, as we aimed to investigate possible factors contributing to the increased postprandial symptoms reported by FD, our data are not ideal to address this issue, and thus should be repeated in a population of patients with clearly abnormal postprandial symptoms. In addition, our FD patients had predominant symptoms of bloating and fullness, both symptoms that have been associated with antral distension, whereas only a small group of FD patients had predominant early satiety (n = 5), a symptom associated with impaired fundic accommodation. These characteristics could have influenced the results obtained in this study.

In the present study we tried to explain what limits the drinking capacity of FD patients. We hypothesize that the standard meal ingestion in FD leads to earlier filling of the distal stomach, in part secondary to the impaired accommodation of the proximal stomach. The latter, as well as an increased postprandial antral area have been repeatedly shown in FD after the ingestion of a standard meal. Further filling of the stomach, as in our drink test, will further distend the distal stomach until the threshold for discomfort is reached. Recently, evidence was reported that the distal stomach of FD was much more sensitive to filling compared to HV. Therefore, FD will limit further ingestion much sooner than HV to prevent further distention of the distal stomach reflected as a lowered distal stomach volume at the end of the drink test. However, more research is needed before these conclusions can be drawn.

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