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Impaired Drinking Capacity in Patients With Functional Dyspepsia: Relationship With Proximal Stomach Function

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Background & Aims: Impaired fundic accommodation to a meal and hypersensitivity to distention are increasingly recognized as important mechanisms underlying functional dyspepsia (FD). In the present study, we evaluated whether a drink test can predict such abnormalities and thus represent a noninvasive tool to study proximal stomach motor function. *Methods:* Healthy volunteers (HV), nonconsulters with mild dyspeptic symptoms (MS), and patients with FD filled out a disease-specific questionnaire and underwent a drink test with either water or with a high calorie fluid. The maximal ingested volume and the subsequent symptoms were meticulously recorded. In addition, all subjects underwent a gastric barostat study assessing meal-induced relaxation and sensation to distention. *Results:* Drinking capacity was not significantly related to any particular dyspeptic symptom. FD were able to consume less water (893 ± 70 mL) and caloric liquid (767 ± 50 mL) compared with HV (water, 1764 ± 120 mL; caloric liquid, 1308 ± 96 mL) or MS (water, 1645 ± 120 mL; caloric liquid, 973 ± 45 mL). Approximately half of the FD had an abnormal water or Nutridrink test compared with 9% of MS and 4% of HV. Furthermore, FD developed significantly more symptoms than MS or HV after both drink tests. The drinking capacity did not predict impaired fundic accommodation or visceral hypersensitivity. *Conclusions:* FD, but not MS, have an impaired drinking capacity to both water and a nutrient liquid. The drinking capacity is not related to a specific dyspeptic symptom and does not predict proximal stomach motor function.

Impaired meal-induced relaxation[1–5] and hypersensitivity to distention[2,3,6–9] of the proximal stomach are suggested as important pathophysiological mechanisms causing dyspeptic symptoms. Recently, sumatriptan, a 5-HT_{1p} receptor agonist that induces fundic relaxation,[3,10] has been shown to enhance accommodation to a meal in patients with impaired meal-induced relaxation resulting in increased caloric intake.[3] Similarly, the κ-opioid agonist fedotozine, shown to increase the threshold for discomfort, resulted in clinical improvement in patients with functional dyspepsia (FD). Clearly, these studies suggest that correction of these abnormalities by fundic relaxant agents and visceral analgesics, respectively, may thus represent new therapeutic strategies to treat certain subgroups of patients with FD.

Ideally, the different subgroups of patients should be identified either by typical symptoms or by a specific diagnostic test before the respective treatment is started. Impaired fundic accommodation is said to be associated with early satiety,[3] implying that the prevalence of this motor abnormality should be high in patients with severe early satiety. However, the specificity of this symptom and its value in clinical practice to predict impaired fundic relaxation is unclear. To date, a gastric barostat study is considered to be the golden standard to evaluate proximal stomach function. It should be emphasized, however, that a gastric barostat study is invasive, time consuming, and uncomfortable and therefore is not suitable for routine clinical practice. Recently, a caloric drink test was reported to assess the symptom of early satiety,[3] suggesting that nutrient meal intake could be a surrogate marker of fundic relaxation. Also, distending the stomach with water[11] has been shown to induce symptoms, particularly in patients with FD[11] and bulimia nervosa,[12] again suggesting a putative noninvasive test of gastric sensitivity.[12] However, the relation between these 2 drink tests and proximal stomach function and their value predicting impaired accommodation and/or visceral hypersensitivity has not been adequately studied. Therefore, the present study was designed to investigate the value of a water or nutrient drink test predicting impaired accommodation and/or visceral hypersensitivity.

Abbreviations used in this paper: FD, functional dyspepsia; HV, healthy volunteers; MDP, minimal distention pressure; MS, mild dyspeptic symptoms; NDI, Nepean Dyspepsia Index.

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Materials and Methods

Subjects

Subjects without any abdominal complaints or with very mild dyspeptic symptoms who did not consult a physician, and with no previous abdominal surgery and taking no medications, were asked to participate in the study. In addition, patients from the outpatient clinic or patients referred to the endoscopy unit for upper endoscopy were included if they fulfilled the new Rome criteria of FD[13] and if endoscopy was negative, i.e., no organic abnormality possibly explaining the dyspeptic complaints was encountered during the endoscopy. If nondominant reflux-like symptoms were present, gastroesophageal reflux was excluded by 24-hour pHmetry. Patients on acid-suppressive drugs had to stop medication at least 5 days before the study. Drugs known to affect gastrointestinal motility were stopped at least 48 hours before the study.

All subjects gave written informed consent before the study. The study protocol was approved by the Medical Ethical Committee of the Academic Medical Center, Amsterdam, The Netherlands.

Symptom Questionnaire

All subjects were asked to fill out the Nepean Dyspepsia Index questionnaire, a recently developed disease-specific questionnaire.[14] Briefly, it evaluates 15 symptoms related to FD over the last 2 weeks. All 15 symptoms are scored on their frequency of occurrence (from 0 to 4 with 0 = not at all and 4 = every day/almost every day), the degree of intensity (rated from 0 to 5 with 0 = not present and 5 = very severe), and degree of bothersomeness (from 0 to 4 with 0 = not at all and 4 = extremely severe). The total scores of each symptom were then added yielding a total symptom score or the Nepean Dyspepsia Index (NDI). Subjects with an NDI score ≤ 5 were considered as healthy volunteers (HV). Volunteers with mild symptoms (the total symptom score between 5 and 25) but not consulting a physician, were considered as non-patients with mild dyspeptic symptoms (MS). Based on the study by Talley et al.,[14] individuals with an NDI score ≥ 25 were classified as having FD.

Drink Test

On 2 separate days and after an overnight fast, subjects were asked to drink every minute 100 mL of water or a nutrient liquid (Nutridrink, N.V. Nutricia, Zoetermeer, The Netherlands; 1.5 Kcal/mL, 39% fat, 48% carbohydrates, 13% protein). After each 100 mL, symptoms of satiety, epigastric bloating, nausea, and pain were scored on a scale from 0 to 5 with 0 = no sensation, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe or discomfort. When a score of 5 was reached, the test was ended and the number of beakers emptied $\times$ 100 was recorded as the maximal ingested volume. Thereafter, the subjects were asked to score the same symptoms at 1 and 2 hours after the end of the drink test.

Gastric Barostat

Proximal gastric motility was assessed by means of an electronic barostat. After anesthesia of the throat (10% xylocaine spray), subjects swallowed a 1200-mL polyethylene bag, tightly wrapped on the distal end of a double lumen polyvinyl tube (12 ch, Salem Sump tube; Sherwood Medical, St. Louis, MO). The balloon was unfolded by inflation of 500 mL of air and was positioned in the proximal stomach by gently withdrawing the tube until slight resistance was felt. The tube was connected to the barostat and fixed to the cheek, and subjects were positioned upright. The barostat automatically corrected for the compressibility of air (Medtronic Functional Diagnostics, Stockholm, Sweden). Intraballoon pressure and volume were recorded continuously during the evaluation, and data were stored on a personal computer, using commercially available software (Polygram for Windows; Medtronic Functional Diagnostics, Stockholm, Sweden).

Study Protocols

Study 1. Healthy volunteers with an NDI score ≤ 5 were selected and asked to participate in both a water and a Nutridrink drink test. These data were used to determine normal values and to evaluate possible gender differences.

Subjects were asked not to smoke or consume alcohol for at least 24 hours before the study. After an overnight fast, they were asked to drink water or Nutridrink at a rate of 100 mL/min. Symptoms were scored after every 100 mL as described above and maximal volume ingested was recorded.

Study 2. Subjects were asked to fill out the NDI questionnaire, to participate in both the water and the Nutridrink drink test, and to undergo a barostat study. All tests were done on separate days, after an overnight fast and after stopping acid-suppressive medications and drugs known to interfere with gastrointestinal motility. The order of the tests was randomized.

The protocol of the drink tests was identical as described in protocol 1. In addition, subjects were asked to record bloating, satiety, nausea, and pain 1 and 2 hours after the end of the test.

The barostat protocol consisted of 2 parts: the first part consisted of the distention protocol evaluating visceral sensitivity to distention, whereas the second part evaluated the meal-induced fundic relaxation. After introduction, unfolding, and positioning of the balloon, an adaptation period of 15 minutes was introduced. Thereafter, minimal distention pressure (MDP) was determined as the pressure required to obtain an intraballoon volume $>$ 30 mL. Subsequently, the proximal stomach was distended using a stepwise distention protocol with steps of 2 mm Hg lasting 2 minutes. After 1 minute, symptoms of bloating, satiety, nausea, and pain were scored on a scale from 0 to 5 with 0 = no sensation and 5 = discomfort 1 minute after the pressure step. The pressure was increased until discomfort was reported, then the procedure was immediately terminated. The balloon was deflated for 30 minutes followed by a 30-minute period at MDP + 2 mm Hg to assess basal fundic volume. Next, a 200-mL nutrient liquid meal

(Nutridrink) was consumed within 1 minute using a straw, and fundic volume was recorded for the following 60 minutes. Again, bloating, satiety, nausea, and pain were scored every 5 minutes using the same scale.

Statistical Analysis

Based on the NDI scores, subjects were classified in 3 groups: healthy volunteers, nonpatients with mild symptoms, and patients with FD. The symptoms reported at the end of the drink tests and during follow-up were analyzed for each individual symptom (bloating, satiety, nausea, and pain). In addition, these symptom scores were summated yielding an aggregate total symptom score at each time point (at the end of the drink test, and at 1 and 2 hours after the test).

In the barostat studies, the threshold for discomfort was determined as the maximally tolerated pressure during the gastric distention protocol. Data are presented as mean ± SEM.

Basal and postprandial volumes were measured as the mean volume of 5-minute periods using commercially available software (Polygram for Windows; Metronics, Stockholm, Sweden). The relaxation after ingestion of the liquid meal was expressed as the difference in volume between the mean volume of the total postprandial recording period (60 minutes) and the 15 minutes before meal ingestion. Symptoms reported during the postprandial period are expressed as mean values for every time point. In addition, symptoms reported during the entire postprandial period were added to give the total symptom score of each individual symptom (bloating, satiety, nausea, and pain). The sum of these scores gave the total postprandial symptom score.

Data are expressed as mean ± SEM. The Student t test for paired or unpaired observations or a one way analysis of variance (ANOVA) (Bonferroni for multiple comparison) were used to compare the means. The χ^2 test was used to compare the occurrence of symptoms or abnormal tests between the different groups of patients. A P value < 0.05 was considered statistically significant.

To investigate the relation between symptoms and the data obtained from the functional tests, both the total score of each symptom (severity, frequency, and bothersomeness) as well as the score of severity alone were considered. The Pearson correlation was calculated as a descriptive tool, and a multivariable stepwise (backward selection) logistic regression analysis was performed using commercially available software (S-Plus 2000; Math Soft, Seattle, WA).

Results

Subjects and Symptoms

To determine normal values, 44 healthy volunteers with an NDI score ≤ 5 (HV, 24 women and 19 men; age, 20–54 years) were invited to participate in study 1 and underwent both the water and the Nutridrink test.

Seventy-eight subjects agreed to participate in study 2. Nine subjects were included after exclusion of increased acid exposure. At 24 hours of pHmetry, pH was <4 in 1.9% ± 0.7% of time. Based on the NDI score, 25 HV (14 women and 11 men; age, 20–46 years), 11 subjects with mild symptoms (8 women and 3 men; age, 20–46 years) and 42 patients with FD (31 women and 11 men; age, 19–63 years) were identified and had both drink tests and a gastric barostat study. Body weight did not differ between the 3 groups (HV, 69.6 ± 2.6 kg; MS, 64.4 ± 2.5 kg; and FD, 63.2 ± 2.1 kg). The mean total NDI score of the HV was 1.2 ± 0.4, compared with 13.1 ± 1.5 for the mild dyspeptics and 91.5 ± 5.5 for the FD. At baseline, none of the HV reported moderate, severe, or very severe complaints on any of the 15 symptoms. In contrast, 6 of the 11 MS had 1 moderate to very severe symptom. All of the FD had at least 1 symptom that was scored moderate or severe or very severe on the scale of severity.

Gastric Barostat

Sensitivity to distention. Minimal distention pressure did not differ between the 3 groups (HV, 7.6 ± 0.4 mm Hg; MS, 8.0 ± 0.5 mm Hg; FD, 7.6 ± 0.4 mm Hg). The threshold for discomfort was significantly lower in the FD (9.8 ± 0.5 mm Hg) compared with MS (15.1 ± 1.8 mm Hg) and HV (13.8 ± 0.7 mm Hg). No HV had a threshold for discomfort lower than 10 mm Hg above MDP. Therefore, a threshold of discomfort ≤8 mm Hg was considered as abnormal. Using this cutoff, 1 of 11 (9%) MS and 19 of 42 (48%) FD had an abnormal threshold for discomfort ($P = 0.0001$, χ^2) and were therefore considered hypersensitive.

Fundic accommodation to a meal. The study had to be stopped prematurely in 2 subjects of the FD group because of discomfort after ingestion of 200 mL of the nutrient drink.

Basal volume did not differ between the 3 groups (HV, 286 ± 23 mL; MS, 288 ± 30 mL; FD, 246 ± 18 mL). Meal-induced increase in fundic volume was 158 ± 23 mL in FD compared with 183 ± 33 mL in HV and 212 ± 57 mL in MS (NS). When 64 mL was considered as the lower limit of the normal range (3), 24% of HV, 27% of MS, and 40% of FD had impaired fundic accommodation (NS).

Postprandial symptoms: comparison between HV, MS, and FD. When the scores of each symptom reported during the entire postprandial period were summated, FD had significantly higher scores for bloating, satiety, nausea, and pain (Table 1). Similarly, the sum of all symptoms during the postprandial period was significantly higher in the FD compared with MS and HV.

Table 1. Summated Scores of Postprandial Symptoms During the Gastric Barostat Study

	Bloating	Nausea	Satiety	Pain	Total
HV	13.4 ± 2.3	4.6 ± 1.6	13.9 ± 2.1	0.7 ± 0.5	32.6 ± 5.0
MS	9.0 ± 3.3	6.2 ± 1.6	11.1 ± 3.5	5.0 ± 3.0	31.3 ± 9.4
FD	32.0 ± 2.3[a]	25.8 ± 2.4[a]	30.5 ± 2.6[a]	26.8 ± 2.5[a]	115.6 ± 8.0[a]

NOTE. Symptoms are shown as mean ± SEM.
[a]$P < 0.05$, significantly different from HV and MS, one way ANOVA.

The 90th percentile of the sum of all symptoms was 65. When this value was considered as the upper limit of normal, 8% of HV, 9% of MS, and 78% of FD had an abnormal total symptom score.

Drink Tests

Maximal volume. *Normal values.* Men consumed significantly more water (2084 ± 181 mL vs. 1367 ± 97 mL; $P = 0.0001$) and more Nutridrink (1405 ± 81 mL vs. 946 ± 74 mL; $P = 0.002$) compared with women. Both men and women drank significantly more water than Nutridrink ($P = 0.0001$). When the 10th percentile was considered as the lower limit of the normal range, volumes ≤1100 mL of water for men and ≤800 mL of water for women were considered abnormal. Similarly, volumes ≤800 mL of Nutridrink for men and ≤600 mL for women were considered abnormal.

Comparison between HV, MS, and FD. FD (918 ± 68 mL) consumed significantly less water than the HV (1764 ± 114 mL) and the MS (1645 ± 120 mL). In contrast to water, FD (770 ± 47 mL) and MS (973 ± 45 mL) consumed less Nutridrink compared with the HV (1308 ± 96 mL) (Figure 1). The volume of Nutridrink consumed was markedly lower than that of water in both the HV and MS ($P = 0.0001$). This difference between water and Nutridrink was clearly smaller in FD compared with the 2 other groups.

When the normal limits as determined in study 1 were considered, 4% of HV, 9% of MS, and 64% of FD (χ^2; $P = 0.0001$) had an abnormal water drink test. Similarly, 12% of HV, 9% of MS, and 48% of FD had an abnormal Nutridrink drink test (χ^2; $P = 0.013$). Both drink tests were abnormal in 4% of HV, 9% of MS, and 41% of FD (χ^2; $P = 0.006$).

No significant differences in maximal ingested volume were present between FD with visceral hypersensitivity or impaired fundic relaxation and FD with a normal barostat study.

Relationship between the water and the Nutridrink drink test. There was a significant correlation between the maximal volume ingested in the water test and the Nutridrink test (Figure 2). The correlation coefficient was 0.67 ($P < 0.0001$) for the whole study group, 0.59 ($P < 0.0001$) for the HV, 0.61 ($P = 0.026$) for the MS, and 0.57 ($P < 0.0001$) for the FD.

Relationship between maximal ingested volume, body weight, length, and body mass index. In all groups, there was a significant difference in length (HV, 183 ± 2 cm vs. 171 ± 2 cm; MS, 182 ± 2 cm vs. 169 ± 1 cm; FD, 183 ± 1 cm vs. 167 ± 2 cm) and body weight (HV,

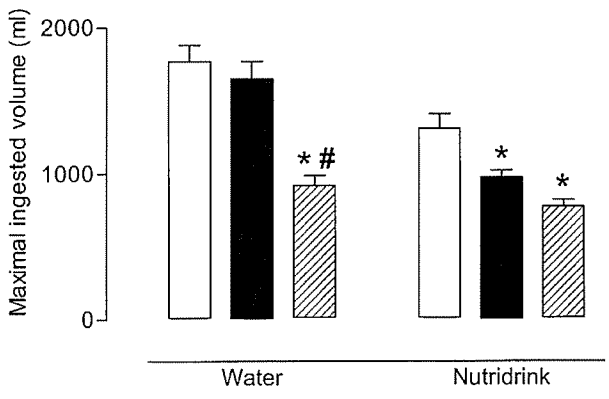

Figure 1. Maximal ingested volume of water and Nutridrink in HV (□), MS (■), and FD (▨). Data are shown as mean ± SEM. *$P < 0.05$, significantly different from control; #$P < 0.05$, significantly different from MS; analysis of variance.

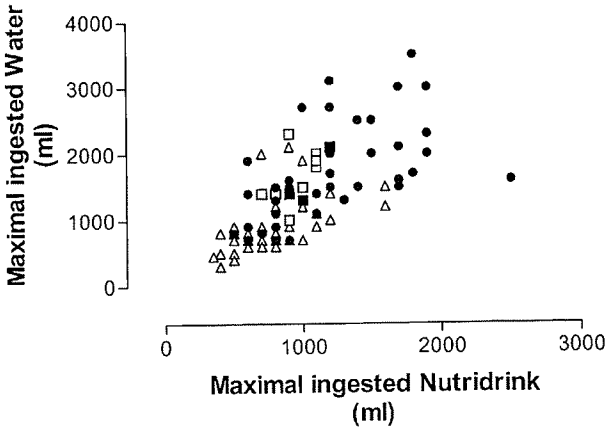

Figure 2. Individual data showing the relationship between the maximal ingested volume of water and Nutridrink in HV (●), MS (□), and FD (△).

77 ± 3 kg vs. 63 ± 2 kg; MS, 71 ± 2 kg vs. 62 ± 2 kg; FD, 73 ± 2 kg vs. 59 ± 2 kg) between men and women, but not in body mass index (data not shown). Interestingly, only a relationship between maximal ingested volume and weight, length, and body mass index was found in HV (body weight: water $r = 0.57$, $P < 0.0001$; Nutridrink, $r = 0.55$, $P < 0.0001$; length: water, $r = 0.57$, $P < 0.0001$; Nutridrink, $r = 0.42$, $P < 0.0001$; body mass index: water, $r = 0.34$, $P = 0.04$; Nutridrink, $r = 0.46$, $P = 0.004$), but not in MS or FD (data not shown).

Symptoms during follow-up. HV reported mainly bloating (water, 3.9 ± 0.4; Nutridrink, 3.6 ± 0.4) and satiety (water, 4.8 ± 0.1; Nutridrink, 4.7 ± 0.3) at the end of both drink tests (Figure 3). Pain was almost absent at the end of the tests (water, 0.2 ± 0.2; Nutridrink, 0.2 ± 0.1), whereas nausea was equally reported after water (2.1 ± 0.5) as after Nutridrink (2.0 ± 0.5). After 2 hours, HV did not report any symptoms any more after the water test, whereas some degree of satiety and bloating was reported after the Nutridrink test. The total symptom score decreased from 10.4 ± 0.5 immediately after the Nutridrink test to 6.4 ± 1.2 after 1 hour and to 1.9 ± 0.6 after 2 hours. Similarly, symptoms gradually decreased after the water test from 11.1 ± 0.7 immediately after the test to 4.1 ± 1.6 after 1 hour and to 0.3 ± 0.2 after 2 hours.

At the end of the drink test, FD reported more pain compared with the other 2 groups, whereas the other symptoms did not differ. However, as shown in Figure 3, the symptoms of bloating, nausea, pain, and satiety persisted in FD, even after 2 hours, whereas they were almost completely absent in HV and MS. In MS, only satiety and nausea persisted after the Nutridrink test. The total symptom score at 2 hours was significantly higher in FD (water, 7.2 ± 0.9; Nutridrink, 10.7 ± 0.8) compared with MS (water, 1.2 ± 0.6; Nutridrink, 6.2 ± 1.3) and HV (water, 0.4 ± 0.2; Nutridrink, 2.6 ± 0.6).

Relationship between clinical symptoms and drink tests. Figure 4 shows the relationship between the total NDI score and the maximal ingested volume of water and Nutridrink. In the total study population, there was a significant inverse correlation between the total NDI score and the maximal ingested volume of water ($r = -0.59$, $P < 0.001$) or Nutridrink ($r = -0.47$, $P < 0.0001$). However, as shown in Figure 4, this relationship was not present within each of the 3 groups separately, illustrating that the correlation for the total population rather results from the differences between the different groups existing within this population.

Also, the relationship between individual symptoms and the drinking capacity was evaluated. FD with an abnormal water drink test had a significantly higher score of vomiting (4.6 ± 0.9 vs. 1.0 ± 0.7; $P = 0.027$) compared with FD with a normal test. FD with an abnormal Nutridrink test had significantly more symptoms of regurgitation (5.8 ± 1.1 vs. 2.7 ± 0.7; $P = 0.017$) and vomiting (5.5 ± 1.1 vs. 2.0 ± 0.7; $P = 0.015$). All other symptoms, including early satiety, did not differ significantly between the groups. In addition, multivariate analysis failed to identify a relation between any of the 15 symptoms and abnormal drinking capacity.

Relationship Between the Drink Tests and the Gastric Barostat

When all subjects were considered, there was a significant correlation between the threshold for discomfort on distention and the maximal ingested amount of water ($r = 0.48$, $P < 0.0001$) and Nutridrink ($r = 0.36$, $P = 0.001$). No correlation, however, was found between the drinking capacity and the threshold for discomfort within the 3 different groups separately. In contrast to the threshold for distention, no correlations were shown between the drinking capacity and fundic accommodation to a meal.

As shown in Figure 5, subjects with a lower drinking capacity have a lower threshold for pain and are clustered in the left lower corner of the data plot. However, subjects with an abnormal drink test can have a normal sensation to distention, illustrating that an abnormal drink test is not predictive of visceral hypersensitivity. The data plot showing the relation between the ingested volumes and the meal-induced relaxation are diffusely scattered, again showing that the drinking capacity can not be used to predict the degree of fundic relaxation.

With a cut off of 900 mL for women and 1200 mL for men, the sensitivity of the water drink test to detect visceral hypersensitivity, impaired accommodation, or an abnormal barostat (abnormal threshold for discomfort or impaired accommodation) is 68%, 73%, and 71%, respectively. The positive predictive value of the water test to detect visceral hypersensitivity, impaired accommodation, or an abnormal barostat is 48%, 44%, and 80%, respectively. Similarly, with a cut off of 1000 mL for men and women, the sensitivity of the Nutridrink test to detect visceral hypersensitivity, impaired accommodation, or an abnormal barostat (abnormal threshold for discomfort or impaired accommodation) is 75%, 81%, and 80%, respectively. The positive predictive value of the Nutridrink test to detect visceral hypersensitivity, impaired accommodation, or an abnormal barostat is 44%, 41%, and 75%, respectively.

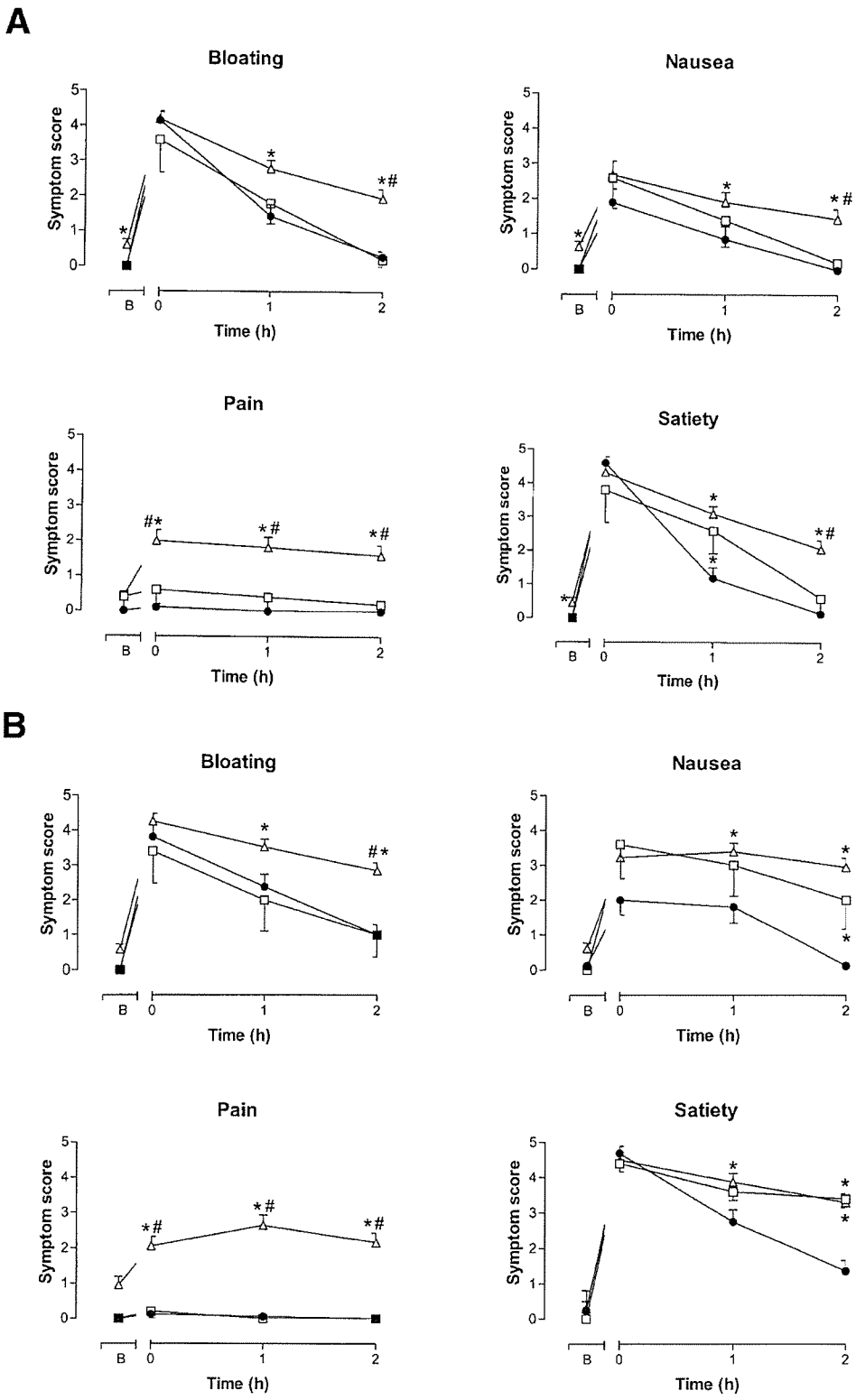

Figure 3. Dyspeptic symptoms of bloating, nausea, pain, and satiety reported by HV (●), MS (□), and FD (△) before (*B*), immediately after, and 1 and 2 hours after (*A*) the water and (*B*) the Nutridrink test. Data are shown as mean ± SEM. $^{*}P < 0.05$, different from HV; $^{\#}P < 0.05$, different from MS, one way analysis of variance (Bonferroni).

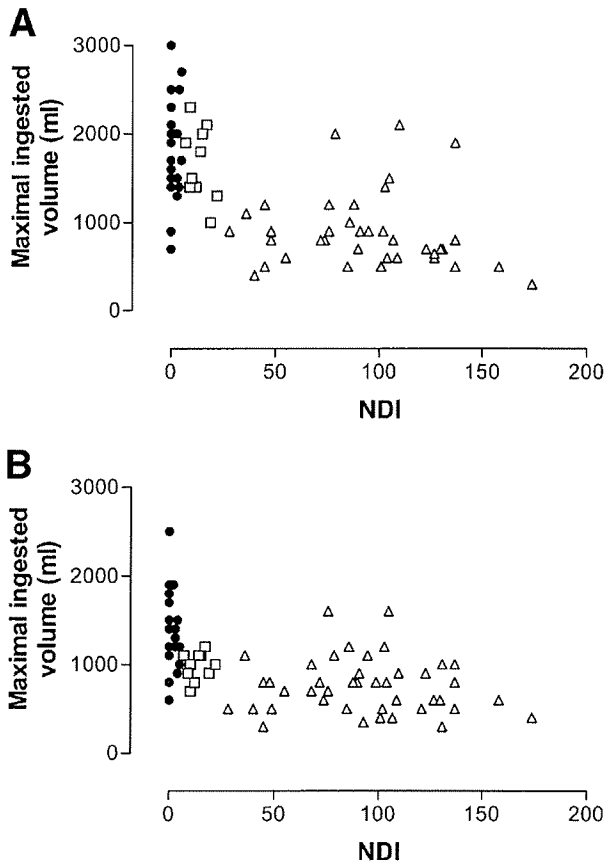

Figure 4. Individual data showing the relationship between the maximal ingested volume of (*A*) water and (*B*) Nutridrink and the total NDI symptom score in HV (●), MS (□), and FD (△).

Discussion

In the present study, we showed that approximately half of the patients with FD have an impaired drinking capacity both for water and for a caloric liquid. In addition, the symptoms after the drink tests were more intense and lasted longer in FD compared with healthy volunteers and subjects with mild dyspeptic symptoms. The drinking capacity was not related to any particular dyspeptic symptom. Furthermore, no relationship was found between the drinking capacity and impaired fundic accommodation or visceral hypersensitivity of the proximal stomach. Consequently, both drink tests have a low sensitivity and specificity predicting these pathophysiological mechanisms. Therefore, our drink tests can not be considered a sensitive noninvasive alternative for gastric barostat studies. At the best, they may prove useful as a standardized test to provoke dyspeptic symptoms and as such to evaluate the effect of new treatments on postprandial symptoms, irrespective of the underlying pathophysiological mechanism.

To date, a gastric barostat study is considered to be the golden standard to evaluate proximal stomach function. However, this is an invasive, time-consuming, and uncomfortable investigation. Recently, loading the stomach with water has been suggested as a simple noninvasive test of gastric sensitivity,[12] and this test induces clearly more symptoms in patients with FD[11] and bulimia nervosa.[12] Similarly, Tack et al.[3] demonstrated impaired intake of a caloric liquid in patients with early satiety and abnormal meal-induced fundic relaxation. Conversely, ingestion of a caloric liquid may thus indirectly assess the magnitude of fundic relaxation. In the present study, we modified both tests and investigated to what extent they can provide information on visceral sensitivity and fundic relaxation.

To determine normal values, healthy subjects with a total NDI symptom score of 5 or lower were selected. This cut off was arbitrarily chosen and implies that also subjects not completely devoid of symptoms were considered as HV. Theoretically, inclusion of these subjects could represent a confounding factor. However, it should be emphasized that the NDI score is a sensitive tool evaluating 15 different symptoms, including some aspecific symptoms like bad breath, resulting in a maximal score of 195. Talley et al. reported that subjects without dyspepsia even have a mean score of 10,[14] illustrating that our HV (mean NDI of 1.2) are a good representation of the population to determine normal values. In HV, the drinking capacity was significantly greater in men compared with women and was significantly related to body weight and length. As expected, HV consumed more water than caloric liquid, most likely as a result of the negative feedback of nutrients entering the small intestine. FD, but not subjects with only mild symptoms, drank significantly less than HV of both liquids. Approximately half of the FD had an abnormal drink test, clearly illustrating an impaired drinking capacity in FD. In contrast to HV, the drinking capacity was not different between men and women, although the difference in body weight and length persisted, suggesting that in FD other factors determining fluid intake become more important.

Under normal conditions, the maximal ingested volume of a caloric liquid depends on the balance between mechanisms increasing gastric volume, such as fundic relaxation, and negative feedback mechanisms reducing gastric emptying and generating meal-induced symptoms. Previously, impaired fundic accommodation, resulting in a decreased reservoir capacity of the proximal stomach, was suggested to be an important mechanism reducing intake of a caloric liquid.[15] However, in the

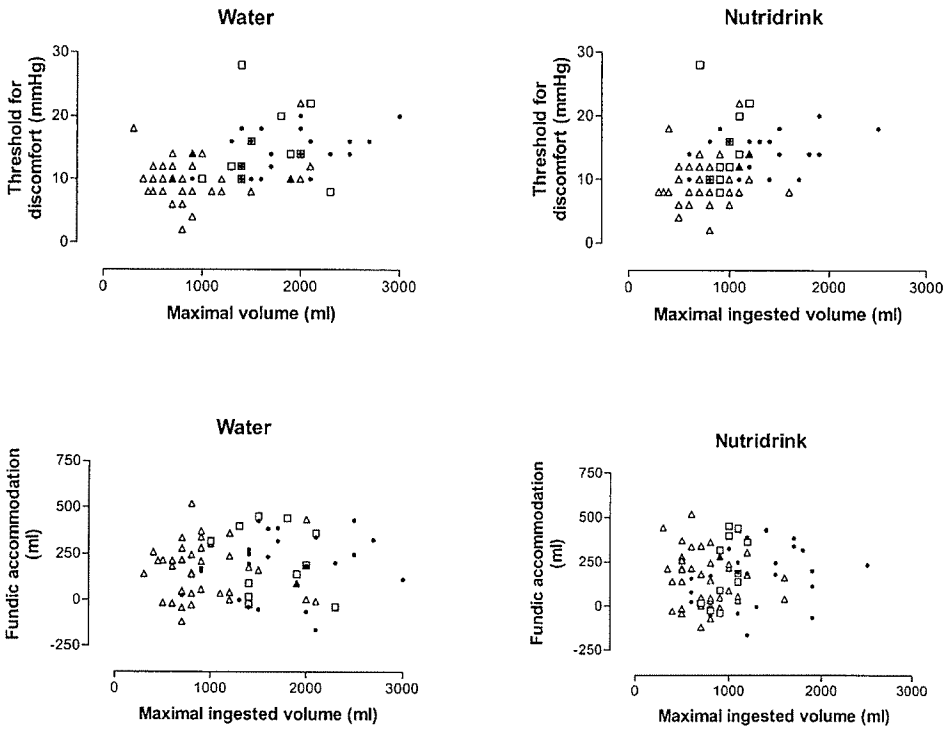

Figure 5. Individual data showing the relationship between the threshold for discomfort and the postprandial fundic accommodation and the maximal ingested volume of water and Nutridrink in HV (●), MS (□), and FD (△).

present study, we found no difference in drinking capacity between FD with a normal gastric barostat study and those with impaired fundic accommodation. There was also no significant relationship between drinking capacity and fundic accommodation, and furthermore, we previously showed that the drinking capacity was not enhanced by fundic relaxation with sumatriptan.[16] Although impaired accommodation to some extent may contribute to impaired drinking capacity, our findings suggest that it is not a major determinant. Alternatively, the threshold to trigger the negative feedback mechanisms may be lowered or, as previously demonstrated, increased sensitivity of the duodenum to nutrients to generate symptoms[16] may be more important factors explaining the impaired intake of Nutridrink in FD.

In the absence of nutrients, other mechanisms (i.e., visceral distention) that limit fluid intake should be considered. Distention of the distal stomach and the duodenum has been shown to trigger comparable vagovagal reflexes, resulting in relaxation of the proximal stomach and inducing sensations of fullness and satiation.[17–20] Most likely, these vagovagal reflexes are activated during the water test. The finding that HV can drink more water than caloric liquid suggests that the feedback mechanisms triggered by nutrients are more pronounced or take place before the distention-mediated reflexes are activated. Interestingly, however, the volume of water ingested by FD, in contrast to HV, was almost similar to that of the caloric liquid. This suggests that intake of a liquid in FD is rather determined by volume than by its caloric content. One explanation may be that the feedback mechanisms triggered by distention are up-regulated in FD, possibly resulting from increased antral distention and/or increased sensation to distention. Recently, increased sensitivity to antral distention was shown in FD,[18] whereas an ultrasound study clearly illustrated that ingestion of water gradually increases the antral diameter, even more in FD compared with HV.[11] However, it is unlikely that antral distention is still present 2 hours after water ingestion and, clearly, other mechanisms like increased sensation to duodenal distention should also be considered.[21,22] Our results illustrate that the interaction between the drink tests and the pathophysiological mechanisms of FD is much more complex than previously suggested. Most likely, many factors such as abnormal perception of the presence of nutrients, changes in wall tension, and increased distention of the proximal gut, against a background of psychological factors, may all contribute. More specific tests evaluating these mechanisms are greatly needed, preferably used in combination to gain more insight in FD.

Ideally, one should be able to identify the pathophysiological mechanism involved to select the drug correcting this abnormality. At present, visceral hypersensitivity and impaired accommodation are assessed by a barostat study. Recently, a drink test has been suggested

as a noninvasive and inexpensive alternative.[3,11,15] Ingestion of a nutrient liquid was shown to correlate specifically with early satiety and to predict impaired accommodation with a sensitivity of 89% and a specificity of 72%.[15] Although we used the same liquid nutrient, sensitivity and specificity to predict impaired fundic accommodation and/or visceral hypersensitivity were lower in our study. This may be explained by the difference in drinking rate between the 2 studies. The drinking rate in the study by Tack et al. is 7 times slower, and therefore the maximal ingested volume may, under these circumstances, be more dependent on other factors, such as gastric emptying. On the other hand, as water quickly empties from the stomach, our drinking rate may have been relatively slow, allowing emptying of a significant proportion during the drinking test. This phenomenon may have contributed to the low sensitivity and predictive value of the water test to predict visceral hypersensitivity. It should be emphasized, however, that there was only a small difference between the volume of water and caloric liquid ingested by FD, suggesting that this phenomenon is rather limited. An alternative explanation for the difference between the water drink test and the barostat results may be that the barostat balloon only distends the proximal stomach. In contrast, ingestion of a liquid distends the whole stomach and, as it leaves the stomach, also the duodenum. Therefore, more regions of the proximal intestine are activated during the drink test. Furthermore, spatial summation is known to heighten perception.[23] This phenomenon may also contribute to the discrepancy between the 2 different tests. To what extent distention of the antrum and/or duodenum during a drink test determines the drinking capacity in FD needs further investigation. Nevertheless, our data suggest that our drink tests do not predict the underlying pathophysiological mechanism and thus can not be considered a sensitive noninvasive alternative for the gastric barostat studies. At best, they can be used as a screening tool to select patients with an abnormal barostat study, irrespective of the underlying mechanism, with a positive predictive value of 75%–80%. This approach may be useful in clinical trials evaluating the effect of a fundic relaxing agent in this patient population. Because approximately one third of FD had a normal barostat, performing a barostat study only in patients with an abnormal water test would reduce the number of normal unnecessary barostat studies. However, because of the low sensitivity of the drink test, many patients with an abnormal barostat will be missed, making this approach less attractive.

One of the most important parameters evaluating therapeutic success should be the change in postprandial symptoms. Drugs altering visceral sensation during gastric distention may not necessarily prove effective in clinical practice. For example, fedotozine increases the threshold for discomfort[24]; however, its therapeutic effect in patients with FD is rather limited.[25,26] A simple test provoking typical symptoms in a standardized way may have practical value evaluating new drugs before embarking on large clinical trials. Loading the stomach with water or a caloric liquid provoked significantly more symptoms in FD compared with HV and MS. Similar findings have been reported previously with a water load test in patients with FD[11] and bulimia nervosa.[12] Whether the water test is superior compared with a caloric liquid test or whether they should be used together remains to be determined. It has to be emphasized, however, that the evaluation of symptoms is complex and prone to subjective interpretation. Nevertheless, a drink test may represent a simple and inexpensive approach to evaluate postprandial symptoms in a standardized manner. Further studies are, however, certainly needed to confirm its value.

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