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UNIVERSITÀ DEGLI STUDI DI TORINO

**Gastric emptying and related symptoms in patients treated with buspirone, amitriptyline or clebopride: a "real world" study by $^{13}$C-octanoic acid breath test**

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**Running title:** Functional dyspepsia and OBT

**Abstract**

**BACKGROUND:** Gastric motility is a key-factor in the pathogenesis of functional dyspepsia (FD). $^{13}$C-octanoic acid breath test (OBT) is a tool used for measuring gastric emptying time in clinical setting. We aimed to investigate the variation in FD symptoms and OBT parameters before and after treatment with buspirone, amitriptyline or clebopride.

**METHODS:** Between Jan-2007 and Dec-2014, we enrolled 59 patients with FD unresponsive to first-line therapy with proton pump inhibitors and/or domperidone that underwent OBT before and after 3 months of buspirone (n=32), amitriptyline (n=16) or clebopride (n=11) treatment.

**RESULTS:** Early satiation severity was positively correlated with gastric half emptying time ($t_{1/2}$) (r=0.3789, p=0.003) and gastric lag phase (r=0.3371, p=0.011), and negatively correlated with gastric emptying coefficient (r=-0.3231, p=0.015). A reduction in $t_{1/2}$ measurement in association to post-prandial fullness, and early satiation severity improvement was observed (p=0.009, p=0.005 and p<0.001, respectively). Patients treated with buspirone obtained both a decrease in $t_{1/2}$ (p=0.005) and an amelioration in early satiation (p=0.001). Patients under amitriptyline treatment experienced an improvement in post-prandial fullness (p=0.046), whereas no variation was reported in patients treated with clebopride.

**CONCLUSIONS:** Patients with FD, non-responders to first-line therapy and reporting meal-related discomfort, may benefit from buspirone or amitriptyline-based therapies.

**Key words:** Breath test - Functional dyspepsia - Gastrointestinal motility

Dyspepsia is a common disorder characterized by upper abdominal discomfort or pain and meal-related symptoms, with a notable impact on quality of life and sense of well-being of affected subjects.[1] In the clinical context, a key issue is the accurate identification of patients with dyspepsia who require further investigation to rule out serious underlying structural diseases.[2] Despite a certain degree of overlapping features, according to Rome IV criteria, functional dyspepsia (FD) is defined as the predominant presence of one or more symptoms including bothersome postprandial fullness or early satiation (post-prandial distress syndrome), epigastric pain (epigastric pain syndrome) or epigastric burning, occurring for the last 3 months with the onset occurring at least 6 months prior to diagnosis, in absence of evident structural disease.[3, 4] While the global prevalence of FD is estimated to be 10-30% worldwide,[3] in Italy, in the general population, it reaches to 11% with unemployment, divorce and smoking, but not *Helicobacter pylori (H. pylori*) infection, being the main cause associated with an increased risk.[5]

The pathogenesis of FD is likely multifactorial and still unclear; however, impaired gastrointestinal motility with delayed gastric emptying, impaired gastric accommodation after ingestion of a meal, and gastric and duodenal hypersensitivity to distension and intraluminal contents, seem to play a role in a substantial group of patients.[6] Although the gold standard for the diagnosis of delayed gastric emptying is gastric scintigraphy,[7, 8] this method has some limitations mainly due to the use of radioactive material. As a consequence, it cannot be performed in pregnant women and may raise some safety concerns in breast-feeding women and young patients. Furthermore, scintigraphy is a relatively expensive procedure not always available outside specialist centers. Therefore, $^{13}$C-octanoic acid breath test (OBT) has been proposed as a reliable alternative indirect method for measuring gastric emptying of solids.[9-11]

Currently, there is no treatment with established efficacy for FD. In the primary care setting, the first-line therapeutic approach is often represented by antacids, proton pump inhibitors (PPI) and/or prokinetic drugs, such as domperidone, according to predominant symptom.[1] Antidepressant, anxiolytic and other prokinetic drugs should be taken into account in patients non-responders to first-line treatment.

The aim of this study was to investigate, in a specialistic setting, the association between FD symptoms and OBT parameters before and after treatment with buspirone, amitriptyline or clebopride, in patients unresponsive to first-line treatment.

## METHODS

### *Patients*

The study was conducted at the third-level Outpatient Clinic of Gastroenterology, Molinette and San Giovanni Antica Sede Hospital, Turin, Italy. The flow chart of the study is depicted in Figure 1. From a total of 870 patients with upper abdominal complaints, who underwent OBT for gastric emptying measurement, between January 2007 and December 2014, we retrospectively enrolled 59 patients with FD diagnosed according to Rome III criteria and unresponsive to first-line therapy with PPI and/or domperidone.[3] To meet the criteria for the definition of FD, patients had to have undergone upper gastrointestinal endoscopy. All included subjects had repeated OBT assessment after 12 weeks of second-line treatment. Seven patients reported a previous history of *H. pylori* infection, with therapy taken more than 6 months before OBT assessment, and eradication confirmed by urea breath test. The remaining patients had negativity *ab initio* for this infection. Data regarding dyspeptic symptoms (bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning) were collected before and after treatment, and scored according to severity (0 = absent, 1 = mild, when the

symptom could not be ignored, but did not influence daily activities, 2 = severe, when the symptom influenced daily activities).[13]

Overall, 32 patients were orally treated for 12 weeks with buspirone 10 mg twice daily, 16 patients with amitriptyline 4.5 mg twice daily for the first 2 days followed by 7.5 mg twice daily for the remaining treatment period, and 11 patients with clebopride 5 mg twice daily before meals for the entire period.

The study protocol was conformed to the Declaration of Helsinki guidelines. Data were managed with respect of patients' privacy. All patients gave their written informed consent prior to treatment.

*$^{13}$C-octanoic acid breath test*

Gastric emptying rate was determined by OBT. All patients were fasted for 12 hours prior to undergoing breath test. Weight and height were assessed, and 2 basal breath samples were collected before meal. The test meal consisted in a muffin (EXPIROGer®, SOFAR, Italy) with a total caloric value of 378 kcal (57 g carbohydrate, 14 g fat, 6 g protein and 100 mg of $^{13}$C-Octanoic acid without gluten, glucose and lactose) and 150 mL of natural water.[9, 11] Afterwards, breath samples were collected in 10 mL plastic tubes every 15 minutes up to a 4-hours period. The ratio of $^{13}$CO to $^{12}$CO was measured in each breath sample by isotope ratio mass-spectrometer (QuinTron Instrument Company, USA).[14] The parameters calculated were gastric half-emptying time ($t_{1/2}$), defined as the time needed by the stomach to metabolize and excrete the half of $^{13}$C-labeled substrate, gastric lag phase ($t_{lag}$), defined as the required time to reach the maximum emptying peak of the $^{13}$C-labeled substrate, and gastric emptying coefficient (GEC), an index that accounts for the rates of both

appearance and disappearance of the label in breath.[15, 16] According to the supplier's instructions, delayed gastric emptying was defined as $t_{1/2}$ of more than 120 minutes.

*Statistical Analysis*

Continuous variables were expressed as median and 95% confidence interval (CI) of the median. Test for normal distribution was performed by D'Agostino-Pearson normality test. Kruskal-Wallis test and chi-squared test were performed to compare basal continuous and categorical variables, respectively. Pearson's correlation coefficient (r) was used to measure the degree of association between two continuous variables. Wilcoxon test and Kendall's coefficient of concordance were used to compare paired continuous and categorical variables before and after treatment, respectively.

For all analyses, a $p<0.05$ was considered significant. All statistical analyses were performed by SPSS software version 22.0 (IBM SPSS Statistics for Windows, Chicago, IL).

**RESULTS**

Basal demographical, clinical data and OBT parameters of the 59 enrolled patients are reported in Table I. Median age was 49.9 years and the majority of patients were females (79.7%). Age distribution was significantly different according to treatment regimen (p=0.034). In particular, patients treated with buspirone were older than those treated with clebopride (54.1 years vs. 37.2 years, p=0.011). Age was positively correlated with early satiation severity (r=0.2633, 95%CI: 0.0077 - 0.4866; p=0.044) and with $t_{lag}$ values (r=0.2680, 95% CI: 0.0055 - 0.4959; p=0.046) and negatively correlated with post-prandial fullness (r=-0.2809, 95% CI: -0.5009 - -0.0267; p=0.031). In addition, a trend towards a correlation between age and $t_{1/2}$ (r=0.2458, 95% CI: -0.0110 - 0.4722; p=0.061) was observed. Body mass index (BMI) was neither associated with clinical and demographical data nor

with OBT parameters. No difference was found in basal OBT parameters according to treatment subgroups ($t_{1/2}$, p=0.438; $t_{lag}$, p=0.260; and GEC, p=0.416). Symptoms severity distribution was significantly different, according to treatment regimen, for early satiation (p=0.006) and a trend could be denoted for epigastric pain (p=0.073), whereas no differences were found for post-prandial fullness and for epigastric burning. In particular, 16 out of 20 patients with severe early satiation, and 7 out of 9 with mild early satiation, respectively, were treated with buspirone. In addition, early satiation severity was positively correlated with $t_{1/2}$ values (r=0.3789, 95% CI: 0.1360 - 0.5788; p=0.003) and $t_{lag}$ values (r=0.3371, 95% CI: 0.0815 - 0.5512; p=0.011) and negatively correlated with GEC (r= -0.3231, 95% CI: -0.5401 - -0.0658; p=0.015).

All patients underwent a second OBT assessment after 90 ± 15 days of treatment. Overall, a significant reduction of $t_{1/2}$ measurement associated to a significant improvement of post-prandial fullness and early satiation severity were observed (p=0.009, p=0.005 and p<0.001, respectively) (Table II and Table III). According to treatment regimen, patients that underwent buspirone-based therapy obtained a significant reduction in $t_{1/2}$ values (p=0.005) and a significant amelioration in early satiation (p=0.001). In addition, a trend toward $t_{lag}$ and GEC amelioration values was found (p=0.085 and p=0.060, respectively). Patients treated with amitriptyline experienced a significant improvement in post-prandial fullness (p=0.046), whereas no significant variation was reported in patients under clebopride therapy in OBT parameters and in symptoms severity.

Three out of 59 enrolled patients reported mild side effects: one under buspirone treatment experienced dizziness whereas other two treated with amitriptyline reported dysgeusia and asthenia, respectively. Nevertheless, none of them stopped treatment.

**DISCUSSION**

This retrospective study, conducted in the real world, explored the effect of buspirone, amitriptyline and clebopride treatment on symptoms severity and OBT parameters in patients with FD diagnosis.

In agreement with previous observations,[17] we found a weak correlation between older age and worse OBT parameters, particularly with $t_{lag}$ (r=0.2680; p=0.046). In addition, age was directly associated with early satiety severity, and had an inverse relationship with the prolonged fullness. It has been hypothesized that older patients have a slow gastric motility due to the decreased number of Cajal cells, a nervous-like cell type involved in electrical rhythmicity generation in smooth muscles.[18]

In contrast to other data, BMI was neither correlated with symptoms severity nor with OBT parameters.[19] However, our cohort included normal-weight patients (BMI was in the normal range of 18.0-24.9 $Kg/cm^2$), therefore we could not assessed the association between symptoms and OBT parameters in over-weight or obese subjects.

Currently, available data regarding correlation between symptoms severity and OBT parameters are controversial.[20] In the present study, we found a significant association between early satiation and all OBT parameters, suggesting that alterations in gastric motility may underlie FD manifestations.

After 3 months of therapy, we found a significant improvement of post-prandial fullness (p=0.005) and early satiation severity (p<0.001) together with a significant $t_{1/2}$ reduction (p=0.009). In particular, buspirone led to early satiation and $t_{1/2}$ improvement (p=0.001 and p=0.005, respectively), and amitriptyline in post-prandial fullness amelioration (p=0.046), whereas no significant variation was observed in patients treated with clebopride. As reported by Tack *et al*, in a prospective randomized trial, buspirone may be most beneficial for patients with meal-related dyspepsia without affecting symptoms characteristics of epigastric pain syndrome. However, the authors did not observe any concomitant significant change in solid emptying time assessed by breath test.[21] In contrast to our

results, Talley *et al*, in a recent multicenter trial, found that amitriptyline appeared to induce benefit mainly in FD patients with ulcer-like pain.[22] Probably, the low number of patients enrolled in our study may result in different findings. Regarding clebopride, the absence of clinical relief emphasized by no variation in OBT parameters could be explained by the feature of included patients already unresponsive to first-line therapy with domperidone. Hence, the use of another prokinetic drug, as rescue treatment, did not led to any symptom improvement.

The main limitation of our study is represented by its retrospective design. All patients were recruited between 2007 and 2014, thus FD diagnosis was set according to Rome III criteria. However, in the setting of FD, only minor changes have been introduced following Rome IV classification. Therefore, we think that patients' classification can be considered valid. In addition, patients' enrolment did not allow us to evaluate symptoms severity by validated scores, such as dyspepsia severity score or visual analogue scale. To clarify the allocation of patients to treatment, it should be highlighted that according to literature, our choice is usually to plan a rescue therapy on the basis of the prevalent symptom,[3] using buspirone in case of meal-related symptoms and amitriptyline when an associated psychological disorder (anxiety, depression or both) can be recognized. Finally, clebopride is used in absence of these conditions or in case of patient's refusal to other treatments. On the other hand, the low number of patient treated with amitriptyline and clebopride may have underpowered the results obtained in our study. In fact, patients treated with amitriptyline experienced an improvement for both symptoms severity and OBT parameters without reaching a statistical significance. However, to our knowledge, this is the largest cohort of patients with FD treated with buspirone that underwent OBT before and after treatment. Moreover, this population reflects what happens in real clinical practice.

An unsolved issue remains the search and the treatment for *H. pylori* infection in FD patients. Although worldwide data are heterogeneous, both in terms of prevalence and post-eradication benefit,[23-25] the European guidelines state that bacterial cure produced long-term benefits in one of 12 patients with *H. pylori* infection and FD, and that this is better than any other treatment.[26] Considering that the choice of the more appropriate treatment should be based on local antibiotic usage, documented antibiotic resistance and outcome data,[27] before starting a long-term treatment, as those reported in our study, the search for the bacterium could be performed. On the other hand, it has been reported that there is no relationship between *H. pylori* infection and gastric emptying in patients with FD.[28]

In conclusion, we found that FD was associated with gastric motility abnormalities detectable by OBT. In addition, there was a relationship between symptoms amelioration and the decrease in gastric solid emptying time. Patients non-responders to first-line therapy with PPI and/or domperidone, reporting meal-related discomfort, may benefit from buspirone or amitriptyline-based therapy with no relevant side effects.

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Table I. *Basal characteristics of the 59 enrolled patients*

| | Total | Buspirone | Amitriptyline | Clebopride | P |
|---|---|---|---|---|---|
| Patient number | 59 | 32 | 16 | 11 | |
| Age, years | 49.9 (44.7-54.6) | 54.1 (45.4-60.7) | 50.6 (38.0-60.4) | 37.2 (26.3-53.5) | 0.034 |
| Gender, M/F | 12/47 | 7/25 | 2/14 | 2/9 | 0.613 |
| BMI, $Kg/cm^2$ | 22.5 (21.6-23.2) | 22.5 (21.5-24.7) | 23.1 (20.7-24.1) | 21.6 (20.5-23.6) | 0.652 |
| OBT | | | | | |
| • $t_{1/2}$, min | 224 (203-338) | 213 (184-327) | 261 (146-422) | 350 (187-569) | 0.438 |
| • $t_{lag}$, min | 113 (94-136) | 94 (81-115) | 135 (81-186) | 138 (79-321) | 0.260 |
| • GEC | 2.5 (2.4-2.6) | 2.6 (2.4-2.7) | 2.5 (2.3-2.7) | 2.5 (2.1-2.5) | 0.416 |
| Symptoms, absent/mild/severe | | | | | |
| • Postprandial fullness | 32/16/11 | 21/8/3 | 7/5/4 | 4/3/4 | 0.234 |
| • Early satiation | 30/9/20 | 9/7/16 | 13/1/2 | 8/1/2 | 0.006 |
| ▪ Epigastric pain | 42/10/7 | 27/2/3 | 8/6/2 | 7/2/2 | 0.073 |
| ▪ Epigastric burning | 38/15/6 | 19/7/6 | 11/5/0 | 8/3/0 | 0.219 |

p values were calculated by Kruskal-Wallis test or by chi-squared test for continuous or categorical variables, respectively.

Abbreviations: F, female; GEC, gastric emptying coefficient; M, male; OBT, $^{13}C$-octanoic acid breath test.

Table II. *Comparison of symptoms severity before (T0) and after therapy (T1) with buspirone, amitriptyline and clebopride*

| | | T0 | T1 | p |
|---|---|---|---|---|
| Total | Symptoms, absent/mild/severe | | | |
| | • Postprandial fullness | 32/16/11 | 35/23/1 | 0.005 |
| | • Early satiation | 30/9/20 | 34/22/3 | < 0.001 |
| | • Epigastric pain | 42/10/7 | 44/13/2 | 0.052 |
| | • Epigastric burning | 38/15/6 | 39/18/2 | 0.248 |
| Buspirone | Symptoms, absent/mild/severe | | | |
| | • Postprandial fullness | 21/8/3 | 22/10/0 | 0.157 |
| | • Early satiation | 9/7/16 | 12/18/2 | 0.001 |
| | • Epigastric pain | 27/2/3 | 28/2/2 | 0.414 |
| | • Epigastric burning | 19/7/6 | 19/11/2 | 0.206 |
| Amitriptyline | Symptoms, absent/mild/severe | | | |
| | • Postprandial fullness | 7/5/4 | 9/6/1 | 0.046 |
| | • Early satiation | 13/1/2 | 13/3/0 | 0.157 |
| | • Epigastric pain | 8/6/2 | 9/7/0 | 0.180 |
| | • Epigastric burning | 11/5/0 | 11/5/0 | 1.000 |
| Clebopride | Symptoms, absent/mild/severe | | | |
| | • Postprandial fullness | 4/3/4 | 4/7/0 | 0.102 |
| | • Early satiation | 8/1/2 | 9/1/1 | 0.157 |
| | • Epigastric pain | 7/2/2 | 7/4/0 | 0.157 |
| | • Epigastric burning | 8/3/0 | 8/3/0 | 1.000 |

p values were calculated by Kendall test.

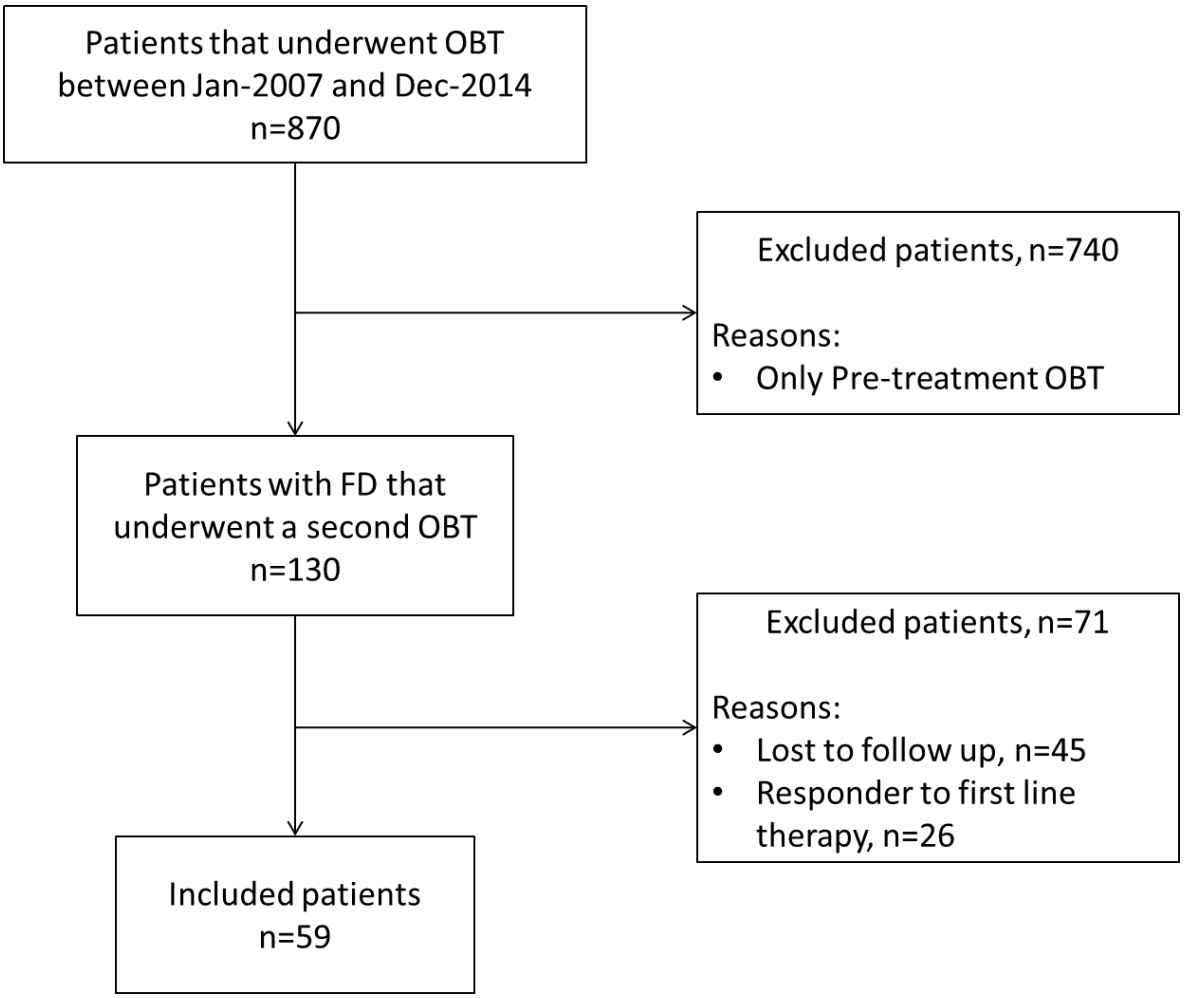
Table III. *Comparison of OBT parameters before (T0) and after therapy (T1) with buspirone, amitriptyline and clebopride*

| | | | T0 | T1 | p |
|---|---|---|---|---|---|
| Total | OBT | | | | |
| | • | $t_{1/2}$, min | 224 (203-338) | 154 (130-186) | 0.009 |
| | • | $t_{lag}$, min | 113 (94-137) | 81 (60-121) | 0.114 |
| | • | GEC | 2.5 (2.4-2.6) | 2.5 (2.4-2.7) | 0.307 |
| Buspirone | OBT | | | | |
| | • | $t_{1/2}$, min | 213 (184-327) | 136 (123-167) | 0.005 |
| | • | $t_{lag}$, min | 94 (81-115) | 62 (42-101) | 0.085 |
| | • | GEC | 2.6 (2.4-2.7) | 2.7 (2.5-2.8) | 0.060 |
| Amitriptyline | OBT | | | | |
| | • | $t_{1/2}$, min | 261 (146-422) | 160 (126-252) | 0.121 |
| | • | $t_{lag}$, min | 135 (81-186) | 88 (59-141) | 0.217 |
| | • | GEC | 2.5 (2.3-2.7) | 2.4 (2.4-2.7) | 0.910 |
| Clebopride | OBT | | | | |
| | • | $t_{1/2}$, min | 350 (187-569) | 249 (105-867) | 0.831 |
| | • | $t_{lag}$, min | 138 (79-321) | 129 (51-461) | 0.492 |
| | • | GEC | 2.5 (2.1-2.5) | 2.2 (1.8-2.7) | 0.359 |

p values were calculated by Wilcoxon test.

Abbreviations: GEC, gastric emptying coefficient; OBT, $^{13}$C-octanoic acid breath test.

Figure 1. *Flow chart of the study*




Abbreviations: FD, functional dyspepsia; OBT, $^{13}$C-octanoic acid breath test.