

¹³C-octanoic acid breath test to study gastric emptying time

G. BRUNO¹, L.R. LOPETUSO¹, G. IANIRO¹, L. LATERZA¹, V. GERARDI¹, V. PETITO¹, A. POSCIA², A. GASBARRINI¹, V. OJETTI¹, F. SCALDAFERRI¹

¹Department of Internal Medicine, Gastroenterology Division, School of Medicine, Catholic University of the Sacred Heart, Polyclinic "A. Gemelli", Rome, Italy

²Institute of Hygiene, School of Medicine, Catholic University of the Sacred Heart, Polyclinic "A. Gemelli", Rome, Italy

Abstract. Digestion is a complex process regulated by several factors. Among these, one of the most important is the time of gastric emptying. A delayed gastric emptying time can be caused by several factors and can generate considerable discomfort in humans. It ranges from mild to real debilitating disorders. Until now, different tests are suggested to study the gastric emptying time. The present review presents the mayor cause and the main symptoms linked to delayed gastric emptying and will focus on the ¹³C-octanoic acid breath test, as a good candidate for studying solid gastric emptying time.

Key words:

Dyspepsia, Gastric emptying time, ¹³C-octanoic acid breath test.

Introduction

The digestion is a physiological process, mediated by a series of chemical and physical transformations. To absorb the carbohydrates, proteins and fats the cooperation of different organs, the release of specific hormones and the activation of numerous enzymes to change these substances in products able to be absorbed and assimilated in the gut are necessary¹. The digestion and the regulation of food intake depend on several factors like quality and quantity of food, perception of food, palatability and the well-being after the meal². This sensation is related to multiple interactions between central nervous system, gastrointestinal tract, liver and adipose tissue^{3,4}. The gut and the stomach have a central role to sense meal volume and composition of food and is able to regulate the appetite⁵. Changes in gastric emptying have the potential to affect the appetite control through the rate of delivery of nutrients to the small intestine⁶.

Gastric emptying is regulated by several factors, such as the nervous stimulations and hor-

mone interactions together with PH, volume, viscosity and composition of food, and individual habits (*i.e.*, smoking, alcohol and stress)⁷. Several gastrointestinal diseases, like Crohn's disease, peptic ulcer, gastric obstruction and gastric cancer⁸⁻¹⁰ can induce delayed gastric emptying. Moreover, other extra-intestinal diseases such as diabetes mellitus¹¹⁻¹³, scleroderma and connective tissue diseases^{14,15}, viral infections¹⁶⁻¹⁹, neurologic diseases²⁰⁻²⁴, autoimmune diseases^{25,26}, psychiatric disease²⁷, rumination syndrome²⁸⁻³² and iatrogenic causes (Alpha-2-adrenergic agonists, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, *octreotide*, *exenatide* and glucagon-like peptide (GLP)-1 agonists, phenothiazines)³³⁻³⁷, gastric and thoracic surgery³⁸⁻⁴¹, can cause delayed gastric emptying.

Clinical indication requesting the study of gastric emptying time

Patients with delayed gastric emptying can show a multitude of symptoms that represents the principal clinical indication to study the rate of gastric emptying. These symptoms include nausea, vomiting (that in some cases contain food ingested several hours before), abdominal pain, early satiety, postprandial fullness, bloating and in severe cases, weight loss^{42,43}. Bloating is common in patients with delayed gastric emptying and is severe in many individuals⁴⁴. The abdominal pain is a frequent symptom, usually is localized to the upper abdomen and is often described as burning, vague, or crampy. In most cases it is exacerbated after meal ingestion but rarely is the predominant symptom⁴⁵. Therefore, these symptoms overlap with those of functional (idiopathic, non ulcer or not *Helicobacter pylori*-related) dyspepsia defined as postprandial fullness, which is one of the most frequent gastrointestinal disorders⁴⁶ and can

cause early satiation, epigastric pain or burning without evidence of structural disease⁴⁷. Moreover, a systematic review, showed that in patients with gastro-esophageal reflux disease the rate of gastric emptying was slowed compared with healthy subjects in about a third of patients. In fact postprandial relaxation of the proximal stomach is augmented or prolonged in gastro-esophageal reflux disease, and this abnormality is associated with the extended presence of the meal in the proximal stomach⁴⁸.

¹³C-octanoic acid breath test to study gastric emptying time

The gold standard to diagnose delayed gastric emptying is the gastric scintigraphy, that provides a physiological, non-invasive and quantitative measure of gastric emptying time⁴⁹. However, this technique has several limitations, due to the use of radioactive material. It is reserved exclusively to departments of nuclear medicine; it requires expensive equipment and the employment of highly qualified staff. Its use is limited to the number of allowed repeatable analyses on the same patient and for the use of pregnant women and children^{50,51}.

Therefore, multiple alternative tests were proposed (Table I), including ¹³C-octanoic acid breath test. Octanoic acid is a fatty acid composed of 8 carbon atoms [CH₃ (CH₂)₆COOH] and is present in fat food. Like all other medium chain fatty acids (MCFA), the octanoic acid is efficiently absorbed from the small intestine and rapidly transported to the liver through albumin serum. In the liver it is oxidated to carbon dioxide, which blends into the pool of plasma bicarbonate and is finally eliminated with breath. Thus, the quantity of ¹³CO₂ in the patient's exhaled breath is a function of the quantity of content leaving the stomach and reaching the intestine^{52,53}.

Since 1993 several groups worked in this field and some correlated the results obtained with scintigraphy. Ghoo et al⁵¹ were the first to analyze this diagnostic tool. All tests were performed after an overnight fast. The test meal consisted of a scrambled egg with the yolk doped with 2 μCi of octanoic acid, sodium salt [^{1-¹⁴C}] (51) was added, beaten, labeled with 3 mCi ^{99m}Tc-albumin colloid (Ultra Technicow; Mallinkrodt Medical, Petten, Netherlands), and baked. The egg was ingested with two slices of white bread and 5 g of margarine, followed immediately by 150 ml of water. In the second series of experiments, however, the yolk was doped

with both 100 mg of [¹³C]octanoic acid (Isotec, Miamisburg, OH, USA) and 2 μCi of [¹⁴C]octanoic acid and sodium salt; yolk and egg white were baked separately but administered together with two slices of white bread. The total caloric value of the meal was 250 kcal. All test meals were consumed in less than 10 minutes.

They assessed an excellent correlation between the gastric emptying coefficient and the scintigraphic half-emptying time ($r = -0.88$); between the half-emptying time determined by the breath test and the scintigraphic half-emptying time ($r = 0.89$); and between the lag phases determined by scintigraphy and those determined by breath test ($r = 0.92$). ¹⁴C can be replaced by ¹³C for labeling the octanoic acid used in the breath test.

They concluded that the octanoic acid breath test is a reliable noninvasive test to measure the gastric emptying rate of solids (51). Another interesting article by Choi et al (50) used a test meal that consisted of two egg whites and one yolk dosed with 100 mg of [¹³C]octanoic acid (Aldrich Co., Milwaukee, WI). The egg whites were mixed with 1-2 mm of Amberlite IRA- 410 pellets (Sigma Chemical Co., St. Louis, MO) labeled with 0.5 mCi ^{99m}Tc-pertechnetate. The yolk and egg whites were cooked separately. The egg meal was placed on a slice of whole wheat bread and given with a glass of skim milk for a total caloric value of 240 kcal and nutrient composition of 35% protein, 40% carbohydrate, 25% fat, and 2.6 g of fiber. In this study parameters from scintigraphy and the breath test were not correlated significantly. Differences of t_{1/2} (for explanation, see next paragraph) between the two tests were highly variable (range for t_{1/2}, 033.1 to 169.6; mean, 48.0 minutes). Increasing breath test "duration" (samples over 4, 5, or 6 hours) yielded decreasing estimates of t_{1/2}. Although widely different values were observed in some subjects, repeated breath tests showed a high degree of reproducibility within individuals (mean coefficient of variation, 12%)⁵⁰.

Afterwards alternative substrates were proposed to study gastric emptying. Perri et al.⁵⁴ compared a muffin meal "EXPIROger" (378 kcal with 57 g carbohydrate, 14 g fat, and 6 g protein and 100 mg of ¹³C-octanoic acid without gluten, glucose and lactose) with the first test meal proposed by Ghoo in a multicenter study on healthy subjects. This study showed similar results on the rate of gastric emptying between the two test meals. Furthermore, EXPIROger's palatability resulted normal in 53% of subjects, good in 39% and bad in only 6% of healthy volunteers⁵⁴.

Table I. Principal diagnostic tests for delayed gastric emptying.

Test	Method
Gastric Scintigraphy	99-m technetium sulfur-colloid labeled low fat, egg-white meal. Scinti-scanning at a minimum of 1, 2 and 4 h after test meal ingestion in the upright position.
Stable isotope breath tests	The non-invasive ¹³ C-labeled octanoate breath test is an indirect means of measuring gastric emptying. It is a medium chain triglyceride which is bound to a solid meal such as a muffin. After ingestion and stomach emptying, ¹³ C octanoate is rapidly absorbed in the small intestine and metabolized to ¹³ CO ₂ which is expelled from the lungs during expiration. The rate limiting step for the signal appearing in the breath is the rate of gastric emptying.
Radiopaque markers	Indigestible markers, i.e. 10 small pieces of nasogastric tubing, none of the markers should remain in the stomach on an X-ray taken 6 h after ingestion with a meal.
Ultrasonography	Emptying measurement of a liquid meal by serially evaluating cross-sectional changes in the volume remaining in the gastric antrum over time.
Magnetic resonance imaging	Using gadolinium to measure semi-solid gastric emptying and accommodation using sequential transaxial abdominal scans.
Single-photon emission CT	⁹⁹ Tc pertechnetate that accumulates within the gastric wall rather than the lumen and provides a three-dimensional outline of the stomach. Measurement of regional gastric volumes in real-time to assess fundic accommodation and intragastric distribution can be made.
Swallowed capsule telemetry	The ingestible “SmartPill®” (VA Boston Healthcare System, MA, USA), or telemetry capsule measures pH, pressure and temperature using miniaturized wireless sensor technology. The time taken for the pill to be expelled from the stomach into the duodenum is measured by monitoring the time point at which the acid readings of the stomach are replaced by the dramatic increase in pH as the capsule enters the duodenum.
Antroduodenal manometry	A water-perfused or solid- state manometric catheter is passed from the nares or mouth and placed fluoroscopically into the stomach and small bowel to measure actual gastroduodenal contractile activity. The frequency and amplitude of fasting, interdigestive and post-prandial contractions can be recorded, and the response to prokinetic agents can be assessed.
Electrogastrography (EGG)	Measurement of gastric slow-wave myoelectrical activity <i>via</i> serosal, mucosal or cutaneous electrodes. It is most conveniently recorded with cutaneous electrodes positioned along the long axis of the stomach.

Moreover, Bromer et al⁵² used a 350-kcal muffin meal (carbohydrate: 63 g, fiber: 3 g, protein: 7 g, fat: 6.8 g) formulated as a powdered mix (Metabolic Solutions, Inc., Nashua, NH, USA in a small, microwavable container. This meal has 18.6% of calories as fat, similar to the fat content of egg meals used in prior breath test studies. One hundred milligrams of [¹³C]octanoate in 60 cc of water were added to the power mix. For the purposes of this evaluation, 500 Ci of [^{99m}Tc] sulfur colloid was also added to the water. After mixing thoroughly with a disposable spatula, the muffin mixture was microwaved for 2.5 min at 80% power. The muffin was immediately removed from its container, sliced in half, and allowed to cool for 5 mins. The muffin was ingested with 100 cc of water and eaten within 10 min, at which time an additional 50 cc of water labeled with 125 Ci [¹¹¹In] DTPA was ingested.

In this study the OBT for GE, using an easily prepared muffin meal, significantly correlates

with GES for solids. This muffin-based OBT is a sensitive and specific method to detect delayed GE in dyspeptic patients.

Interpreting ¹³C-octanoic acid breath test

¹³C-octanoic acid breath test provides an indirect measure of gastric emptying time as the appearance of ¹³CO₂ in the breath is determined by the gastric emptying, digestion, absorption and metabolism subject's capacity of octanoic acid⁵⁵. The analysis requires the collection of two breath samples immediately before the ¹³C-octanoic acid breath test meal (time 0) and then at regular intervals of 15 minutes and for the next 4 hours⁵⁴, the determination of the ratio ¹³CO₂/¹²CO₂ that can be performed by mass spectrometry (IRMS) or infrared spectrometry (IR) (56). To avoid false positive or false negative data, the patient should be fasting at least 8 hours before the test, drinking only non-carbonated water. During the examina-

Table II. ^{13}C Octanoid Breath Test: methodology.

Step 1	Fasting: 8 hours before. Only natural water allowed
Step 2	Two breath samples collection (Time 0).
Step 3	Weight and Height Assessment
Step 4	^{13}C -labeled meal assumption with 250 ml of natural water.
Step 5	Breath sample collection each 15' for 4 hours (no drinking, eating, smoking, sleeping or doing physical exercises).
Step 6	Samples analysis through mass spectrometry (IRMS) or infrared spectrometry (IR).
Step 7	Results discussion and therapy evaluation with the patient.

tion it doesn't allow drinking, eating, smoking, sleeping or doing physical exercises (Table II). According to Ghoo et al, to evaluate the ^{13}C -octanoic acid breath test is necessary to determine two main parameters: $t_{1/2}$ and Gastric Emptying Coefficient (GEC), that related to peak rate of meal metabolism. Input data for making calculation of these parameters, include height and weight of subjects performing the test. $T_{1/2}$ is defined as the time (number of minutes) needed by the stomach to metabolize and excrete the first half of ^{13}C -labeled substrate. A cumulative excretion of ^{13}C of one-half of the ingested amount is considered normal (between 70 and 120 minutes), while gastric emptying time is considered slowed when the $t_{1/2}$ exceeded the 120 min^{54,57-60}.

Discussion

The ^{13}C -octanoic acid breath test appears to be a valid examination, compared with scintigraphy, to study the rate of gastric emptying. The advantages offered by this type of examination are multiple. In fact ^{13}C -octanoic acid breath test is a non invasive, safe, simple, repeatable test, that can be used in pregnant women and in children. There are no physiological states or diseases that contraindicate a ^{13}C breath test. It is indicated in those patients who have dyspepsia-like symptoms and can serve to evaluate whether those symptoms are due to a real delay gastric emptying. It is able to justify the prescription of prokinetic drugs in patients undergoing abdominal, gastric, thoracic or bariatric surgery. It can be used in diabetic subjects to evaluate the presence of gastroparesis; in gastro-esophageal reflux, to assess dietary modification and functional foods that could normalize or improve gastric

emptying time. However, there is not always concordance between symptoms and gastric emptying disorders and the interpretation of breath test results may also be influenced by technical factors such as characteristics and concomitant diseases of patients, the test meal used (caloric content, nutrient composition, meal size, solid or liquid phase), the duration of breath collection, and the cut off limits of the normal data. New test meals with ^{13}C -octanoic acid were proposed, for example by mixing the powder together with the muffin just before the ingestion. This approach avoids the step of cooking ^{13}C octanoic acid. Furthermore, patients with delayed gastric emptying should be further investigated to identify intestinal or extra-intestinal causes, possibly through an upper endoscopy or excluding an active infection by *Helicobacter Pylori*.

Conflict of interest

None of the Authors declares conflict of interest

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