

^{13}C -octanoic acid breath test in functional and organic disease: critical review of literature

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Abstract. – The ^{13}C -octanoic acid breath test is considered a useful tool to measure gastric emptying both in physiological and pathological conditions.

Many studies have concerned functional dyspepsia. Recently, breath test has been used in predicting a delayed gastric emptying in subsets of dyspeptic symptoms. In detail only postprandial fullness and vomiting are resulted significantly correlated with delayed solid emptying.

Besides in the patients with dyspepsia and irritable bowel syndrome associated, intestinal disturbances did not seem to contribute to delay gastric emptying.

In diabetic patients octanoate test has confirmed the percentages of delayed emptying obtained by means of scintigraphy. In other organic states (celiac disease, cirrhosis, renal failure, neurological disease, etc) most of reports have proved a delayed emptying of solids.

In GERD and ulcer disease gastric function is resulted normal, being accelerated in distal gastrectomy and in *hyperemesis gravidarum*. From pathophysiological point of view *Helicobacter pylori*, extrinsic autonomic neuropathy (apart from diabetes) and autoimmunity do not seem to relate with gastric emptying, both in functional and organic disease.

Key Words:

Gastric emptying, ^{13}C breath test.

Introduction

Breath test using the nonradioactive isotope ^{13}C bound to a digestible substance, has been validated for measuring gastric emptying (GE) of solids¹. The octanoate breath test (OBT) provides reproducible results that correlate with findings of gastric emptying scintigraphy².

The published peer-reviewed literature on OBT in functional and organic disease has been searched on PubMed using the key words ^{13}C breath test, octanoic acid and gastric emptying. The more significant referenced articles from recent published manuscripts and abstracts from national and international meetings have been included in this review, apart from pharmacological studies which have been instead excluded.

Functional Disease

Although gastric dysmotility and dyspeptic symptoms are often associated, their relationship remains unclear. The aim of many studies has been to evaluate the relationship between GE and clinical features in functional dyspepsia (FD). In 1996, by means of the scintigraphic method, Stanghellini et al³ have demonstrated that female sex, relevant and severe postprandial fullness, and severe vomiting were independently associated with delayed GE of solids in patients with FD.

More recently OBT has been utilized to verify these clinical evidences.

Table I summarizes the results of the more important published reports about percentage of delayed GE and relationship with symptoms in FD.

In 1998, Perri et al⁴ have confirmed that a delayed GE was associated with postprandial fullness, nausea, and vomiting. On the contrary a successive study has showed that symptom prevalence and severity were similar in dyspeptic patients with and without delayed GE⁵. Specific symptoms did not seem to be of predictive value for identifying alterations of GE.

In the opposite direction, a more recent report has confirmed previous evidences. In 393 patients, a multivariate analysis has

Table I. Prevalence of delayed emptying and relationship with symptoms in functional dyspepsia in literature studies.

Study	Pts	% delayed GE	Correlations
Stanghellini et al., 1996 (scintigraphy)	343	34	Associated with female sex, postprandial fullness, vomiting
Perri et al., 1998	304	33	Associated with postprandial fullness, nausea and vomiting
Sarnelli et al., 2003	392	23	Associated with postprandial fullness, nausea and vomiting
Talley et al., 2001	551	24	No correlation

showed that the presence of vomiting and postprandial fullness was associated with delayed solid emptying⁶.

Another interesting question has concerned the association of FD with irritable bowel disease (IBS). Gastric emptying of digestible solids in IBS patients has been evaluated in few studies. In a scintigraphic study, overlapping dyspepsia was diagnosed in 66% of 146 IBS patients. IBS patients without overlapping dyspepsia had normal gastric emptying of solids⁷. A significant association was observed in IBS patients between delayed gastric emptying and overlapping relevant postprandial fullness and nausea. More recent reports using OBT have obtained conflicting results. Haag et al⁸ have showed a GE significantly delayed both in dysmotility-like dyspeptic patients and in IBS subjects, although the sample size was small in both cases.

Helicobacter pylori status did not correlate with delayed GE. Conversely in a large series (309) of FD where the patients were divided in two groups (54% were FD alone and 46% FD with overlapped IBS), GE, accommodation to meal and *Helicobacter pylori* infection did not differ in the two populations. Association between FD and IBS was more frequent in female patients and was characterized by a greater symptom severity⁹.

Organic Disease

OBT has been successfully utilized in different pathological conditions (Table II). Numerous studies have evaluated gastric function in diabetes mellitus. Various reports have demonstrated similar results using OBT when compared to scintigraphy¹⁰. These data have confirmed that solid GE was delayed in 30-50% of diabetics. Other

studies have evaluated the relationship between GE and glycemic levels, autonomic neuropathy and gastric autoimmunity. In particular De Block et al¹¹ have showed that solid GE was delayed in 42% and liquid emptying in 36% of type 1 diabetics. Gastric motility did not correlate with symptoms and HbA(1c) level was the only risk factor for delayed solid emptying. Parietal cell antibodies did not correlate with GE while autonomic neuropathy correlated with liquid emptying only.

In other organic diseases most of reports have demonstrated a delayed GE. For instance in cirrhosis 75% of 80 subjects displayed a delay of GE¹². In another study where GE was also delayed, paracentesis did not influence gastric behaviour¹³.

As expected, in neurological conditions such as Parkinson and amyotrophic lateral sclerosis, GE was significantly slower than in control groups^{14,15}.

These pathological evidences, compared to healthy controls, were confirmed in 16 obese women, in 30 critic ill subjects and in 5 post colectomy ileostomic patients¹⁶⁻¹⁸.

The OBT has also been employed to study the effects of renal failure on the gastric performance. Diabetic chronic renal failure patients have displayed lower gastric emptying rates than non-diabetic nephropatic patients. Even the non-diabetic patients had a significantly delayed GE rate compared to the healthy volunteers¹⁹. In a successive report 66 hemodialysis patients, 58 predialysis patients and 28 on peritoneal dialysis patients were included. Gastroparesis was most prevalent in patients on peritoneal dialysis²⁰.

Children with celiac disease have been studied by OBT before and after gluten free

¹³C-octanoic acid breath test in functional and organic disease: critical review of literature**Table II.** The main published peer-reviewed literature on OBT in organic diseases.

Disease	Yrs	Journal	Pts	Cts	Methods	Results	Comments
Diabetes	2003	Diab Care	42	/	AN+ & Pcas - and GERD	40% delayed	
Preterm child	2003	Nutrition	16	/		vs milk	physiology
	2004	J Pediatr	10	/		body position	physiology
Obesity	2004	Diab Ob Met	16	16		delayed	female
Celiac disease	2000	Acta Paed	9	9	Pre and post GFD	delayed	children
Cirrhosis	1999	Hepato-gastroenterology	80	/	<i>H. pylori</i> NS	75% delayed	
	2002	Eur J GastrHep	Ns	Ns	Paracentesis NS	delayed	+ dialyzed
GERD	2002	Gut	36	/		normal	children
Gastrectomy	1994	Gastroenterology	Ns	Ns	Distal gastrect.	accelerated	abstract
	2003	Am J Gastroenterol	16	12	Post cancer	Billr II sympt. NS	+ barostat
Ileostomy	2000	Dig Dis Sci	5	5	Post colectomy	delayed	
Parkinson	2005	Neurosci Lett	36	22		delayed	
Am lat sclerosis	1999	Digestion	18	14		delayed	
Duodenal ulcer	1996	Dig Dis Sci	17	15	<i>H. pylori</i> NS	normal	
Critic ill	2001	Critic Care	30	22		delayed	
Renal failure	2001	Clin Nephrol	62	27		delayed	
	2002	Clin Nephrol	58	28 PD	66 HD	delayed in PD	<i>H. pylori</i> NS
Hyper. gravidarum	1994	Gastroenterology	Ns	Ns	vs no dyspeptic	accelerated	abstract

Abbreviations: yrs, years; pts, patients; cts, controls; AN, autonomic neuropathy; Pcas, parietal cell antibodies; GFD, gluten free diet; NS, not significant; ns, not specified; Billr, Billroth II symptomatic vs asymptomatic; PD, peritoneal dialysis; HD, hemodialysis.

diet²¹. GE was significantly delayed when compared with healthy controls. After 6 months of gluten free diet, emptying values returned to normal range.

Although GE has commonly been considered altered in gastro-esophageal reflux disease (GERD)^{22,23}, infants with GERD did not have delayed GE using the OBT²⁴. In healthy preterm infants right-side positioning was associated with increased triggering of gastro-esophageal reflux, despite accelerating GE²⁵. In a physiological study, the gastric emptying rate for individual neonates was independent of milk amount²⁶. Also in duodenal ulcer disease OBT has showed normal emptying results²⁷. However, in some case, GE can be accelerated such as in distal gastrectomy²⁸, although in a recent report²⁹, in patients with post cancer distal gastrectomy, emptying rate was within normal range. No differences were found between symptomatic and asymptomatic Billroth II subjects.

Finally during recovery from *hyperemesis gravidarum*, the patients have showed accelerated GE compared to no dyspeptic pregnant women³⁰.

Discussion

Several mechanisms concur to GE such as gastric accommodation and tone, antral contractility, antroduodenal coordination, pyloric function, entero-enteric reflex and probably digestive hormone modulation. By means of OBT, numerous attempts have been made to demonstrate some pathogenetic role on gastric function of various extrinsic factors. The concept that an inflammation of the stomach could compromise gastric function has been took often into account³¹. However the majority of studies have excluded an association between *Helicobacter pylori* infection and gastric function, both in functional^{4,8,9} and organic diseases^{12,20,27}.

Besides a few reports have evaluated the impact of the autoimmunity on GE and generally only in diabetes and with conflicting results¹¹.

Manometric antral hypomotility has been associated with scintigraphic gastric stasis³². These data are consistent with the hypothesis that the delayed GE in gut dysmotilities occurs because of impaired antral peristalsis due to antral hypomotility or increased resistance to flow into the small bowel due to intestinal dysmotility. On the other hand, in a more recent work using OBT, there was no positive correlation between symptom scores, gastric half emptying times and motility scores³³.

Finally, always after OBT, half-time GE was delayed in 6 out of 12 patients with primary autonomic neuropathy (AN)³⁴. In diabetic patients another study concludes that the ¹³C-octanoic acid breath test represents a suitable measure of delayed GE, which is associated with the severity of gastric symptoms and with extrinsic cardio-vascular AN³⁵. Apart from diabetes it is however unlikely that an extrinsic AN can play a decisive pathophysiological role in gastro-intestinal disorders³⁶.

Although the published reports about OBT are numerous and qualified both in physiological and pathological conditions and confirm reliability, accuracy and safety of this test, more studies are needed to further demonstrate the real significance and utility of gastric function tests.

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