

Novel and Validated Approaches for Gastric Emptying Scintigraphy in Patients with Suspected Gastroparesis

Michael Camilleri · Andrea Shin

Received: 30 April 2013 / Accepted: 2 May 2013 / Published online: 22 May 2013
© Springer Science+Business Media New York 2013

Controversy exists regarding the relation of upper gastrointestinal symptoms to gastroparesis, which centers on the reportedly weak correlation between symptoms and gastric emptying (GE) measurements. Appropriate management of patients with suspected gastroparesis thus requires the use of validated assessments of GE.

GE scintigraphy (GES) using a low-fat EggBeaters (chicken egg white) meal (ConAgra Foods Inc., Omaha, NE, USA) [1] is regarded as the gold standard due to standardized procedures, methods, and well-established normal values. Although this meal has the advantage of good tolerability by the majority of symptomatic patients, there are potential drawbacks: a few patients may not tolerate any solid meal, or the low fat and caloric content may not be able to adequately stress the system, failing to identify impaired gastric motor function in a subset of individuals. Therefore, identification of an alternative, appropriate test meal may be important for clinical and research applications.

In this issue, Sachdeva et al. [2] compared GE of the low-fat EggBeaters solid meal (255 kcal containing 2 % fat, 24 % protein, 72 % carbohydrate, and 2 % fiber) to an Ensure Plus (Abbott Laboratories, North Chicago, IL, USA) liquid meal (350 kcal containing 28 % fat, 15 % protein, 57 % carbohydrate, and no fiber) to identify a valid alternative for patients unable to consume the standard low-fat egg-white meal. On separate days, 20 healthy volunteers participated in a well-designed prospective study comparing GES with these two meals; simultaneously, the authors evaluated gastric contractility using a

wireless motility capsule (WMC) during both assessments. The objectives were to demonstrate feasibility and to provide hypothesis-generating data (e.g., definition of coefficient of variation [COV; standard deviation/mean] to facilitate the design of future studies).

The conclusion that GE of a liquid nutrient meal is similar to that of low-fat egg-white meal (of similar calorie content) is valid, at least in healthy subjects. Nevertheless, as acknowledged by the authors, their results will require replication in a larger cohort, and in subjects with suspected gastroparesis who might differ from a healthy population in terms of having differential GE of solid versus liquid meals. Jones et al. [3] previously reported a significant but weak ($r = 0.42$, $p < 0.01$) correlation between GE of solids and nutrient-containing liquids among 86 patients with diabetes mellitus. In the study by Sachdeva et al. [2], the correlation between the GE $T_{1/2}$ of the two meals was similarly weak ($r = 0.53$) among healthy subjects, suggesting that there are significant intra-individual differences in the emptying of the two meals, and that less than 30 % of the variance is attributable to the same mechanisms for emptying of the two types of meals.

It is also necessary to clarify the inter-individual COV with the EggBeaters and the liquid nutrient meal. Diagnostic interpretation of GE $T_{1/2}$ by GES in an individual patient requires robust definition of the intra-individual COV with the specific meal used. Thus, the estimated COV_{inter} for GE $T_{1/2}$ was 25 % with the EggBeaters meal and 24 % using a meal of higher fat and calorie content [4] in which the solid phase is radiolabeled. With the latter radiolabeled solid meal, the COV_{inter} for GE at 4 h was 9.6 %, confirming the recommendation by Tougas et al. [1] that the percent retention at 4 h is an endpoint useful for gastroparesis screening. Similarly, others have shown greater sensitivity of detection of abnormal GE with use of

M. Camilleri (✉) · A. Shin
Mayo Clinic, Charlton 8-110, 200 First St. S.W., Rochester,
MN 55905, USA
e-mail: camilleri.michael@mayo.edu

the 4-h endpoint [5]. Conversely, the COV_{inter} and COV_{intra} for GE $T_{1/2}$ with the 296 kcal, 32 % fat meal were both ~ 25 % [4], suggesting that a single observation of GE $T_{1/2}$ could only be useful as a screen for gastroparesis if the GE $T_{1/2}$ is >150 min (since the median and mean values in 319 patients were 120 and 121.7 min, respectively).

It is also important to recognize that the physical nature of the meal utilizes different motor mechanisms and results in different patterns of emptying from the stomach (Fig. 1). Thus, significant temporal differences between GE of the solid and liquid nutrient test meals in the current study may be attributable to the need for trituration of solids, after initial accommodation, as well as the higher fat content of the liquid nutrient meal which may have retarded GE, particularly at the later stages in the GE process. The authors propose that, with study of a wider range of GE rates, correlation between the results from the two meals will be improved. Nonetheless, it is also possible that differences in the intragastric distribution of the meal, as well as times to trituration of digestible solids may actually be magnified in patients with gastroparesis (and antral hypomotility), further differentiating the results obtained with the caloric liquid meal and the solid meal. Thus, until a comparison study of the two meals has been performed in patients with gastroparesis, the equivalence of these meals remains uncertain.

In contrast to the accompanying study that reported similar patterns of emptying of the easily triturable egg-white meal and liquid nutrient meal of similar caloric content, Horowitz et al. [6] reported previously that nutrient liquids emptied in a monoexponential pattern in comparison to the relatively linear emptying of solids; yet, those meals were of markedly different caloric and fat content. This observation highlights the unresolved

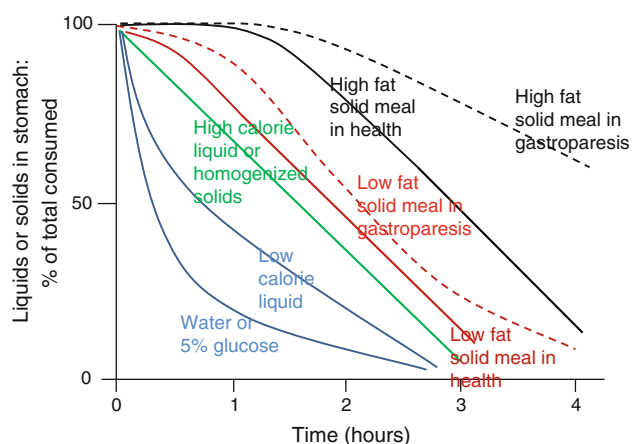


Fig. 1 Patterns of gastric emptying of liquids and solids in health and in gastroparesis. Gastric emptying curves for liquid and solid meals were derived based on data from the available literature (references 1, 2, 4, 5, and 6 in the paper)

question of whether the low-fat, EggBeaters meal is even the optimal solid meal substrate; indeed, significantly different emptying between the EggBeaters meal and a radiolabeled liver at 3 h was reported in the original report “validating” the EggBeaters meal [1]. GES also has utility in the evaluation of the motility effects of drugs, such as has been reported for studies utilizing the 2 % fat EggBeaters meal [7, 8] and with the higher-calorie (296 kcal) and 32 % fat scrambled eggs meal [9, 10].

Given these considerations, we believe it is pertinent to ask: is it time to consider moving to test meals of higher caloric and fat content rather than trying to replace the EggBeaters meal with an Ensure Plus meal? Such a test meal with two eggs, 296 kcal, and 32 % fat content has been extensively validated in the literature, including detailed performance characteristics in large healthy populations [4], responsiveness to treatment with pharmacological agents [9, 10], and demonstrated utility in the clinical practice of three Mayo Clinic sites for over two decades. These studies also demonstrated that the gastrointestinal tract of healthy females empties on average 15 % slower than males [4], an observation that should be factored into the interpretation of GE data.

Patients in the study by Sachdeva et al. [2] were also concurrently evaluated using the WMC in a clever attempt to assess motor function concomitant with the emptying of the two meals. Others have reported that pressure profiles measured with the WMC may prove useful in identifying significant differences in motility indices between healthy volunteers and patients with gastroparesis [11]. Yet, as Sachdeva et al. [2] noted, the relevance of the WMC-measured profiles is unclear due to the potential differences and uncertainty of capsule location, which may be influenced by gastric meal content and distribution. Regional movement of the meal was significantly different between the low-fat EggBeaters meal and liquid nutrient meal in the early stages of GE [2] as has been reported previously [12]. Taken together, these observations suggest that similarities in motility indices for the solid and liquid nutrient meals as measured by WMC testing should be interpreted with caution.

In summary, findings from this study provide important documentation that a liquid nutrient meal empties at about the same rate as an easily triturated solid meal of comparable caloric content. These findings require replication in female and male patients with suspected gastroparesis in order to demonstrate the clinical utility of this alternative radiolabeled meal in the measurement of GES. The pitfall that the low-fat EggBeaters meal may not constitute a sufficient “stressor” to the gastric motor system and hence has low sensitivity in the diagnosis of gastroparesis is not addressed by using the Ensure Plus meal. Indeed, similarities in the GE of the EggBeaters and Ensure Plus meals in

healthy individuals should inform future investigations regarding whether the EggBeaters meal is optimal for the assessment of GE in patients with upper gastrointestinal symptoms. While the Ensure Plus meal may be useful in conducting GES in patients unable to tolerate a solid meal, the published validation data [4] and responsiveness to pharmacological therapy [9, 10] suggest that an alternative meal of higher caloric and fat content should be used to assess GE in the majority of patients with upper gastrointestinal symptoms.

Conflict of interest None.

References

1. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low-fat meal: establishment of international control values. *Am J Gastroenterol*. 2000;95:1456–1462.
2. Sachdeva P, Kantor S, Knight LC, Maurer AH, Fisher RS, Parkman HP. Use of a high-caloric liquid meal as an alternative to a solid meal for gastric emptying scintigraphy. *Dig Dis Sci*. (Epub ahead of print). doi:10.1007/s10620-013-2665-2.
3. Jones KL, Horowitz M, Wishart MJ, Maddox AF, Harding PE, Chatterton BE. Relationships between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. *J Nucl Med*. 1995;36:2220–2228.
4. Camilleri M, Iturrino J, Bharucha AE, et al. Performance characteristics of scintigraphic measurement of gastric emptying of solids in healthy participants. *Neurogastroenterol Motil*. 2012;24:1076–e562.
5. Ziessman HA, Bonta DV, Goetze S, Ravich WJ. Experience with a simplified, standardized 4-hour gastric-emptying protocol. *J Nucl Med*. 2007;48:568–572.
6. Horowitz M, Maddox A, Bochner M, et al. Relationships between gastric emptying of solid and caloric liquid meals and alcohol absorption. *Am J Physiol*. 1989;257:G291–G298.
7. Tougas G, Earnest DL, Chen Y, Vanderkoy C, Rojavin M. Omeprazole delays gastric emptying in healthy volunteers: an effect prevented by tegaserod. *Aliment Pharmacol Ther*. 2005;22:59–65.
8. Shin A, Camilleri M, Busciglio I, et al. Randomized controlled phase Ib study of ghrelin agonist, RM-131, in type 2 diabetic women with delayed gastric emptying: pharmacokinetics and pharmacodynamics. *Diabetes Care*. 2013;36:41–48.
9. Manini ML, Camilleri M, Goldberg M, et al. Effects of Velusetrag (TD-5108) on gastrointestinal transit and bowel function in health and pharmacokinetics in health and constipation. *Neurogastroenterol Motil*. 2010;22:42–49, e7–8.
10. Camilleri M, Vazquez-Roque MI, Burton D, et al. Pharmacodynamic effects of a novel prokinetic 5-HT receptor agonist, ATI-7505, in humans. *Neurogastroenterol Motil*. 2007;19:30–38.
11. Kloetzer L, Chey WD, McCallum RW, et al. Motility of the antroduodenum in healthy and gastroparetics characterized by wireless motility capsule. *Neurogastroenterol Motil*. 2010;22:527–533, e117.
12. Piessevaux H, Tack J, Walrand S, Pauwels S, Geubel A. Intra-gastric distribution of a standardized meal in health and functional dyspepsia: correlation with specific symptoms. *Neurogastroenterol Motil*. 2003;15:447–455.