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Indirect vs direct assessment of gastric emptying: A randomized crossover trial comparing C-isotope breath analysis and MRI

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Abstract

Background: Indirect methods to assess gastric emptying (GE), such as ^{13}C breath tests (BT), are commonly used. However, BT usually use a sampling time of 4+ hours. The current study aims to assess the validity of BT for four liquid meals differing in physicochemical properties. To this aim, we compared them to MRI GE-measurements.

Methods: Fifteen healthy males (age 22.6 ± 2.4 years, BMI 22.6 ± 1.8 kg/m^2) participated in a randomized 2 × 2 crossover experiment. Test foods were liquid meals, which were either thin/thick and 100/500 kcal, labeled with 100 mg of ^{13}C-octanoate. GE was measured with MRI and assessed by ^{13}C recovery from breath. Participants were scanned every 10 minutes and at six time points breath samples were collected up to t = 90 minutes. Two curves were fitted to the data to estimate emptying half-time ($t_{50\ Ghoos}$ and $t_{50\ Bluck}$). T_{50} times were ranked per participant and compared between methods.

Key Results: On average, MRI and BT showed similar t_{50} rankings for the four liquid meals. In comparison to MRI, $t_{50\ Ghoos}$ overestimated, while $t_{50\ Bluck}$ underestimated GE time. Moreover, more viscous foods were overestimated. In most participants individual t_{50} time rankings differed significantly between methods.

Conclusions & Inferences: BT can assess relative emptying differences on group level and collecting breath data for 90 minutes constitutes a lower burden for participants and the research facility. However, BT has severe shortcomings compared to MRI for individual GE assessment. Notably, food matrix effects should be considered when interpreting the results of BT.

KEYWORDS
breath, gastric emptying, isotope, MRI

1 | INTRODUCTION

Gastric emptying (GE) is an important element of gastrointestinal physiology. For clinical applications, highly accurate measurements of GE on an individual level are required for diagnosis.[1] In a research setting GE measurements are often used to determine group differences in GE between treatments (for example.[2,3]

Gastric emptying can be measured directly or indirectly. Direct methods include echography, scintigraphy, and MRI.[4] MRI has been validated as an accurate method to measure GE[5]; it allows accurate real-time visualization and determination of gastric content without

Abbreviations: ^{13}C t_{50}, ^{13}C gastric emptying half-time; BT, breath testing; DOB, delta over baseline; GE, gastric emptying; MRI t_{50}, MRI gastric emptying half-time; MRI, magnetic resonance imaging; TGV, total gastric volume.

the γ-radiation burden of scintigraphy. An exponential curve can be fitted to MRI gastric content measurements over time, from which the half-emptying time (t_{50}) can be estimated.[6,7]

With indirect methods, the emptying process is estimated by labeling the meal with a tracer. Tracer recovery via breath—or blood for acetaminophen[8]—is used as a proxy to estimate GE.[9] Breath testing (BT) is performed with a carbon isotope (^{13}C), which is absorbed and metabolized into CO_2. ^{13}C recovery in breath is used to estimate GE t_{50} using an exponential β function or a Wagner-Nelson function.[9] The advantage of BT is that it requires less expensive equipment and is less invasive than direct methods. Disadvantages are that it provides a proxy measure which may be influenced by other factors and that sampling time is long.

It has been advocated by Bluemel et al.[10] to only use ^{13}C-acetate BT with prior validation by MRI. They demonstrated an overestimation for the exponential β curve fit and an underestimation for the Wagner-Nelson curve fit, in a comparison of the t_{50} of a 300-mL meal. This was measured by MRI and BT using 100 mg ^{13}C-acetate. It was suggested that these differences were caused by dilution by gastric secretions and the composition of the meal.[10] Accordingly, tracer interactions with fat components in a test meal have been shown to affect tracer absorption and subsequent excretion[11] and thus tracer-based estimates of GE.

Sanaka et al.[9] propose a sampling period of at least 4 hours, and in specific pathological cases up to 6 hours, to allow accurate curve fitting. However, this sample collection duration is both a practical limitation and a burden for the participant or patient. Longer sample collection duration may increase accuracy but this may not always be necessary. With liquid foods, recovery differences are apparent within 2 hours post ingestion.[10,12] Apparently, liquid meals empty relatively quickly, especially if their macronutrient content is low.[13] Therefore, for quick emptying foods a much shorter breath sampling time may be sufficient to detect differences.

The current study aims to compare GE over 90 minutes measured by ^{13}C breath analysis and MRI with 4 liquid meals, varying in energy load and viscosity. We hypothesized that food properties will affect GE as measured by both BT and MRI, and that ^{13}C breath analysis will show comparable group results to MRI.

Key Points

- Our aim was to assess similarity in assessment of gastric emptying between 90-minute ^{13}C breath analysis and MRI among four liquid meals.
- On group level both measurement methods show similar order of emptying times, however, both t_{50} times and rankings within a participant differed significantly between methods.
- Ninety minutes of sample collection with BT is sufficient to detect differences in GE t_{50} in liquid meals, however, food matrix affects BT and not MRI outcomes.

2 | MATERIALS AND METHODS

2.1 | Ethics

The procedures followed were approved by the Medical Ethical Committee of Wageningen University (NL48059.081.14). This study was registered in the Dutch Trial Registry under number NTR4573. Written informed consent was obtained from all participants before participation. Participants received monetary incentives for participation.

MRI results from the same study have been published elsewhere.[14]

2.2 | Participants

Participants were recruited via e-mail and social media in the Wageningen region. The participants were 15 healthy normal-weight males (age 22.6 ± 2.3 years, BMI 22.6 ± 1.7 kg/m^2). Inclusion criteria were: being male, aged between 18 and 35 years, having a BMI between 18 and 25 kg/m^2, self-reported good general health, willing to comply with the study procedures, willing to be informed of incidental findings. Exclusion criteria were: unexplained weight loss or gain of >5 kg in the last 2 months, oversensitivity for any of the food products used in the experiment, any reported abnormalities of the gastrointestinal tract, use of medication which may influence gastrointestinal function, having contraindications for undergoing an MRI, and being employed or studying at the department of Human Nutrition at Wageningen University.

2.3 | Design

The study had a randomized 2 × 2 crossover design, with four different liquid meals that were different in viscosity (thin vs thick) and energy load (100 kcal vs 500 kcal). Participants visited the lab facilities 4 times for a test session with at least a 48 hour washout period in between. Each participant had his test session always on the same time of the day.

2.4 | Liquid meals

The ingredients for the liquid meals were: cream (AH Basic, Albert Heijn B.V. Zaandam, The Netherlands), dextrin-maltose (Fantomalt Nutricia®, Cuijk, The Nederlands), vanilla sugar (Dr.Oetker®, Amersfoort, The Nederlands), whey powder (Whey Delicious Vanilla, XXL Nutrition, Helmond, the Netherlands), all mixed together with water in order to obtain a liquid meal in which the macronutrients and calories are equally dispersed. The amount of ingredients was manipulated to create a 100 kcal and a 500 kcal variant. Locust bean gum was added to the meal shake to manipulate viscosity of the liquid meals, that is 20 g for the thick 100-kcal, 10 gram for the thick 500-kcal shake. A hundred milligram of ^{13}C-octanoate (Campro

Scientific GmbH, Veenendaal, The Netherlands) was added to all meal shakes to label them for the BT. Ingredients and nutrient composition of the liquid meals can be found in Table 1.

2.5 | Rheological properties of the stimuli

The flow behavior of the four shakes was determined using a rheometer (Anton Paar MCR 502 equipped with concentric cylinders). Viscosities were measured first at shear rates increasing from 0.01 to 1000 s-1 and then at shear rates decreasing from 1000 to 0.01 s-1 at 370C. Sixty measurements points were recorded for each shake with a measurement duration of 10 seconds per point. The viscosity differed greatly between the four shakes. The 100 Kcal/thin shake displayed the lowest viscosity of all samples. At any shear rate, the 500 Kcal/thin shake displayed a higher viscosity than the 100 Kcal/thin shake and a lower viscosity than the 500 Kcal/thick shake. At any shear rate, the 500 Kcal/thick shake displayed a higher viscosity than the 500 Kcal/thin shake and a lower viscosity than the 100 Kcal/thick shake. The 100 Kcal/thick shake had the highest viscosity of all samples at any shear rate (Figure S1).

2.6 | Test session procedures

Participants were instructed to fast for at least 3 hours prior to the test session. They were only allowed to drink water during that time and nothing in the last hour before the session. After arrival participants provided two baseline breath samples and were scanned for baseline stomach content. After this, participants were taken out of the scanner and instructed to consume the shake through a 1-cm diameter straw within 2 minutes. After that, they were positioned in the scanner again in a supine position and remained there for 90 minutes, undergoing a gastric MRI scan every 10 minutes (see Figure 1 for a session overview). in the same time schedule breath samples were obtained at t = 10, 20, 30, 50, 70 and 90 minutes.

TABLE 1 Energy content and nutrient composition of the four liquids per 100 g, participants received 500 g

	Thin 100 kcal	Thick 100 kcal	Thin 500 kcal	Thick 500 kcal
Protein powder, g	4.5	3.9	12.9	12.5
Cream, g	7.5	6.6	21.6	20.8
Dextrin-maltose, g	7.9	6.9	22.8	22
Vanilla sugar, g	6	5.2	3.4	3.3
Locust bean gum, g	0.7	13.1	0.5	4.1
^{13}C-octaonic acid, mg	100	100	100	100
Water, g	73.3	64.2	38.7	37.2
Total, g	100	100	100	100
Energy[a], kJ	84	84	418	418
Energy, kcal	20.2	20.2	100.3	100.3
Carbohydrates, g	2.4	2.4	12	12
Of which mono- and dissacharides	0.4	0.4	2.1	2.1
Fat, g	0.6	0.6	3	3
Protein, g	1.2	1.2	6	6
Fiber, g	0.5	4	0.5	2.5

[a]Nutrient composition of the food stimuli resemble a mixed meal, with 50% of the energy load coming from carbohydrates, 30% from fats, and 20% from protein.

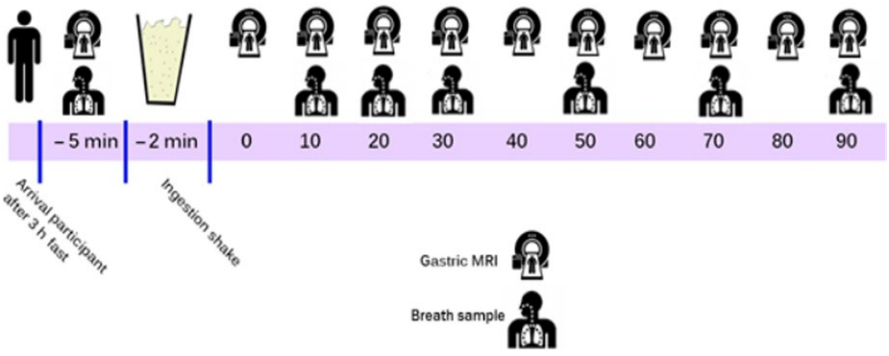

FIGURE 1 Overview of the procedure of one experimental session

2.7 | Direct gastric emptying: gastric content (MRI)

Participants were scanned with the use of a 3-Tesla Siemens Verio (Siemens AG, Munich, Germany) MRI scanner using a T_2-weighted spin echo sequence (HASTE, 24 6-mm slices, 2.4 mm gap, 1.19 × 1.19 mm in-plane resolution). The duration of one scan was approximately 19 seconds, with a breath hold command on expiration to fixate the position of the diaphragm and the stomach. Syngo fastView MRI software (Siemens AG; http://www.healthcare.siemens.com/medical-imaging-it/syno-special-topics/syngo-fastview) was used to manually delineate gastric content on every slice (Figure 2). For each time point, total gastric volume was calculated by multiplying surface area of gastric content per slice with slice thickness, including gap distance, summed over the total slices showing gastric content. Data were fitted using the NLME package in R (R3.2.2; R Foundation for Statistical Computing, Vienna, Austria). The gastric content per time point fitted using a linear exponential model,[6,7] this was subsequently used to determine MRI GE t_{50} (MRI t_{50}).[6]

2.8 | Indirect gastric emptying: ^{13}C expiration (breath test)

Breath samples were collected with single-use one-way valves attached to collection bags (F201-VP-5a; FAN, Leipzig, Germany). Samples were obtained by requesting the participant to exhale through the valve filling the bag to capacity. Breath samples were analysed on the day of sampling on a spectrometer (IRIS 3, ID nr. 109849; Wagner Analysen Technik GmbH, Bremen, Germany). The spectrometer was calibrated before each measurement following the supplier's instruction. Two baseline samples were taken to provide solid baseline ^{13}C concentrations. Subsequently, delta over baseline was calculated for the other time points. The ^{13}C was converted to a percentage of the dose ^{13}C recovered (PDR). The PDR was fitted using the method following Ghoos et al.[15-17] and a more recent modified method by Bluck[7,18] developed for conventional BT data. These formulas were applied to our data to estimate ^{13}C GE t_{50} (^{13}C $t_{50\ \text{Bluck}}$ and ^{13}C $t_{50\ \text{Ghoos}}$) (breathtestcore: Core Functions to Read and Fit ^{13}C Time Series from Breath Tests by Dieter Menne, R package version 0.4.0.9000 (https://github.com/dmenne/breathtestcore)).[10,18-22]

2.9 | Calculations and statistical analyses

All data presented are means and SD unless mentioned otherwise. Significance level was set at a *P*-value of .05. A Sidak adjusted general linear mixed model using treatment and time as factors was used to test main effects on t_{50}. A Sidak corrected post hoc test was performed to test differences between the treatments per time point (IBM SPSS 20 (IBM, Armonk, USA).

A Sidak adjusted general linear mixed model with viscosity and energy load was used to test for the main effects of food composition on t_{50} between treatments (IBM SPSS 20; IBM, Armonk, NY, USA).

Additionally, outcomes were ranked per treatment for each participant. If the ranking between MRI t_{50} and ^{13}C t_{50} were dissimilar Kendall τ distance of the two rankings was computed. Kendall τ distance indicates how many pair-wise swaps are necessary to attain similar rankings. A distance of 0 indicates completely similar rankings, and the maximal distance of six indicates a completely reversed order. Correlation was tested by computing Kendall's τ coefficient.

3 | RESULTS

An overview of the mean t_{50} per treatment, significance of the model factors and post hoc results for both MRI and ^{13}C PDR can be found in Table 2.

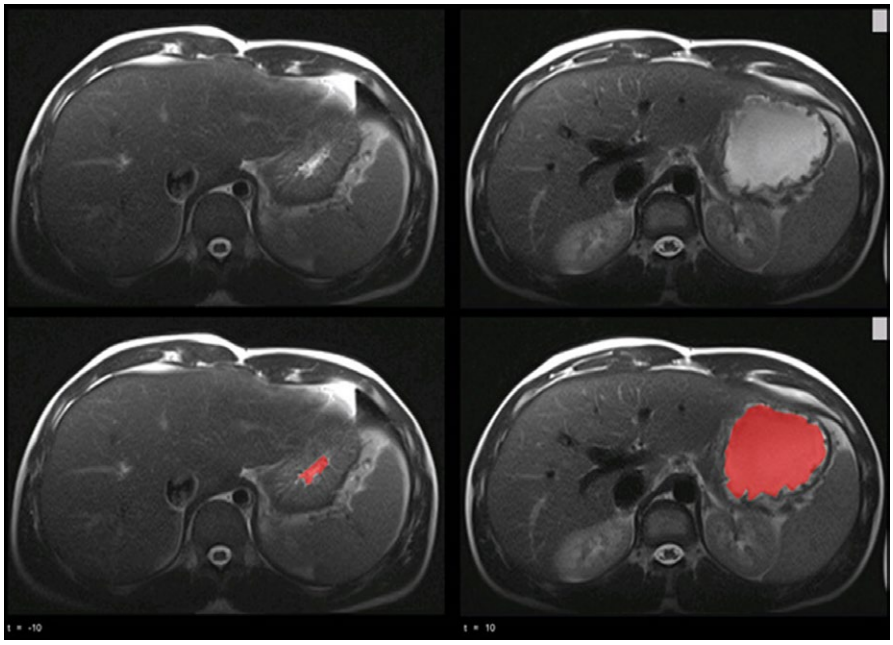

FIGURE 2 Transversal slice at the height of the liver, showing pre-ingestion on the left and 10 min postingestion on the right. The bottom has the surface area of the gastric content highlighted in red. Surface area was used to calculate gastric volume at the moment of a scan

3.1 | Direct gastric emptying: MRI

Total gastric volume over time can be seen in Figure 3. There was a significant effect of viscosity ($P = .006$) and energy load ($P < .001$), but their interaction was not significant ($P = .83$). The thin 100 kcal shake had the shortest GE t_{50} of the treatments (95% CI 11.9-41.4 minutes). The thick 100 kcal had longer GE t_{50} (95% CI 26.4-55.9 minutes), followed by the thin 500 kcal (95% CI 54.9-84.4 minutes). The thick 500 kcal had the highest t_{50} (95% CI 67.3-96.8 minutes). Results show significant effects of energy content for both low ($P < .001$) and high viscosity ($P < .001$). The effect of viscosity was significant for the low energy load ($P = .033$), but not the high energy load condition ($P = .065$).

3.2 | Indirect gastric emptying: ^{13}C Breath test

Percentage dosage recovered over time is shown in Figure 4.

^{13}C $t_{50\ Bluck}$: there was a significant effect of viscosity ($P = .001$), energy load ($P < .001$) and a significant interaction effect ($P = .003$) indicating that the effects of viscosity and energy load are not independent. Breath testing t_{50} was shortest for the thin 100 kcal shake (95% CI 15.1-41.5 minutes). The thick 100 kcal had a longer t_{50} (95% CI 28.6-55 minutes) followed by the thin 500 kcal (95% CI 31.3-57.8 minutes). There was a significant effects of energy load for the low viscosity ($P < .001$) but not the high viscosity condition ($P = .25$). The effect of viscosity was significant for the low energy load ($P < .001$), but not the high energy load condition ($P = .80$).

^{13}C $t_{50\ Ghoos}$: there was a significant effect of viscosity ($P = .003$), energy load ($P < .001$) but no interaction effect ($P = .06$). Breath testing t_{50} was shortest for the thin 100 kcal shake (95% CI 60.1-100.4 minutes). The thick 100 kcal had a longer t_{50} (95% CI 100.9-140.7 minutes) followed by the thin 500 kcal (95% CI 128.9-168.7 minutes). The thick 500 kcal had the highest t_{50} (95% CI 138.5-178.3 minutes). There was a significant effect of energy load for both the low ($P < .001$) and high viscosity condition ($P = .002$). The effect of viscosity was significant for the low energy load ($P = .001$), but not the high energy load condition ($P = .40$).

3.3 | Comparison of BT with MRI

Each session measured with MRI t_{50} and ^{13}C t_{50} is plotted in Figure 5.

Six out of 15 participants showed complete similarity in rankings for ^{13}C $t_{50\ Bluck}$ and six participants had a Kendall distance >1. Four out of 15 participants showed complete similarity in rankings for ^{13}C $t_{50\ Ghoos}$ and 8 participants had a Kendall distance >1.

TABLE 2 Effect of viscosity and energy load on t_{50}

	Thin 100 kcal (min)	Thick 100 kcal (min)	Thin 500 kcal (min)	Thick 500 kcal (min)	Viscosity (*P*)	Energy load (*P*)	Viscosity × energy load (*P*)
MRI t_{50}	27 ± 11^{A}	44 ± 20.7^{B}	69 ± 22^{C}	82 ± 31^{C}	.006	<.001	.83
^{13}C $t_{50\ Bluck}$	27 ± 7^{A}	41 ± 10^{B}	43 ± 7^{B}	44 ± 6^{B}	.001	<.001	.003
^{13}C $t_{50\ Ghoos}$	80 ± 25^{A}	120 ± 26^{B}	149 ± 37^{C}	158 ± 47^{D}	.003	<.001	.06

Different letters indicate Sidak adjusted post-hoc pair-wise comparisons indicated significant differences between the t_{50}.

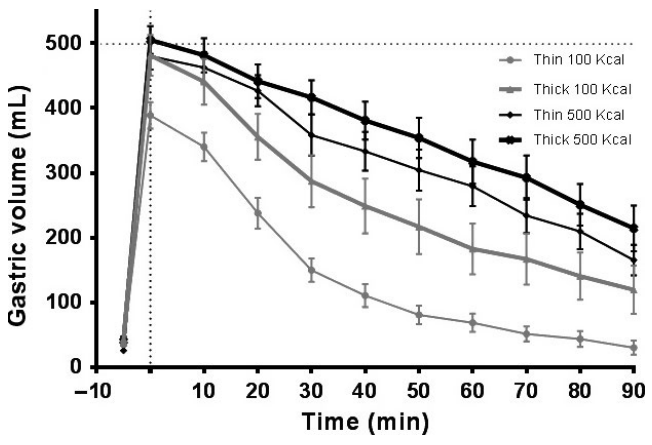

FIGURE 3 Overview of the MRI volume over time of the four treatments (mean ± SEM). These volumes were used to fit emptying curves and extract t_{50}. At time points 0 and 10 the volume of the thin 100 kcal treatment was significantly different from the other treatments, at the following time points there was a significant difference between all but the two 500 kcal treatments

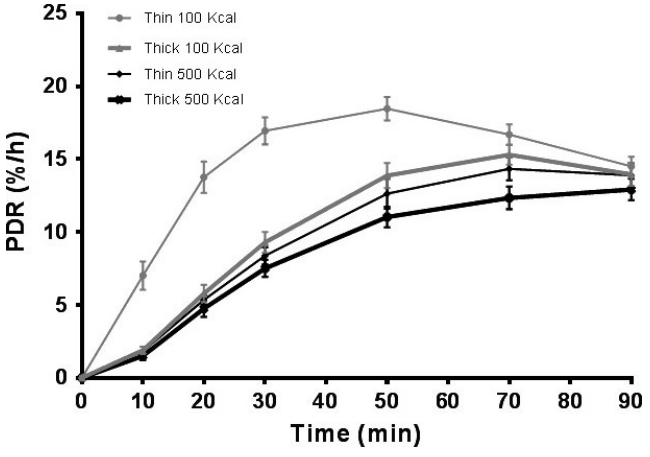

FIGURE 4 Percentage dosage recovered (PDR) over time for the 4 treatments (mean ± SEM). These values were used to derive t_{50}. At time points 10 and 20 the thin 100 kcal was significantly different from all treatments. At 50 and 70 min there were significant differences between the 100 kcal and the 500 kcal treatments. At 90 min there was no difference

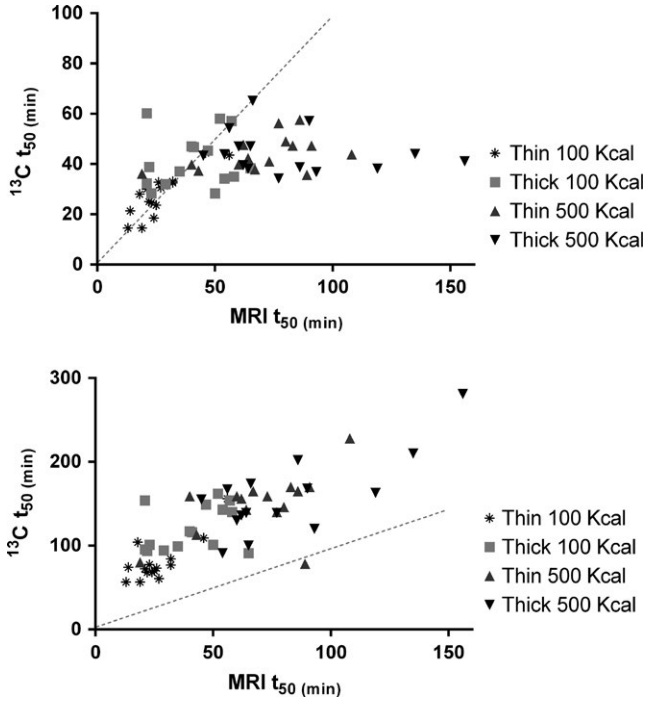

FIGURE 5 MRI t_{50} and ^{13}C t_{50} plotted against each other for all sessions, One dot indicates one session. Scatterplot above shows ^{13}C $t_{50\ Bluck}$ and scatterplot below shows ^{13}C $t_{50\ Ghoos}$. In relation to a linear $x = y$ relationship (grey dotted line) ^{13}C $t_{50\ Bluck}$ underestimated emptying times and ^{13}C $t_{50\ Ghoos}$ overestimated emptying times. Estimated t_{50} values were significantly correlated, with Kendall's $\tau = 0.412$ ($P < .001$) for MRI and ^{13}C $t_{50\ Bluck}$ and Kendall's $\tau = 0.555$ ($P < .001$) for MRI and ^{13}C $t_{50\ Ghoos}$

Estimated t_{50} values were significantly correlated, with Kendall's $\tau = 0.412$ ($P < .001$) for MRI and ^{13}C $t_{50\ Bluck}$ and Kendall's $\tau = 0.555$ ($P < .001$) for MRI and ^{13}C $t_{50\ Ghoos}$.

4 | DISCUSSION

The current study aimed to compare GE times measured by ^{13}C breath analysis and MRI among 4 liquid foods varying in energy load and viscosity by measuring their GE concurrently with ^{13}C breath analysis and MRI over 90 minutes.

Gastric emptying times were increased for the liquid meals by both viscosity and energy load. Although ^{13}C $t_{50\ Bluck}$ underestimated emptying rate, ^{13}C $t_{50\ Ghoos}$ overestimated emptying rate when looking at individual results; only a minority of participants, six for $t_{50\ Bluck}$ and four for $t_{50\ Ghoos}$ had matching rankings. However, on the group level they were similar to MRI t_{50}. Viscosity and energy load showed a significant positive interaction effect for ^{13}C $t_{50\ Bluck}$ which was not apparent when looking at the MRI t_{50} results.

Our ranking data suggest that MRI and ^{13}C t_{50} estimates are congruent on a group level, which is illustrated by the curves shown in Figures 3 and 4. However, individual rankings were different; six participants (40%) had a Kendall distance greater than 1, indicating that there were at least two treatments ranked different in relative GE between measurement methods. From our results we conclude that short-term BT may be a suitable method for relative GE emptying differences in fast emptying food stimuli on a group level, but not for individual estimates.

The outcomes of BT are often used to diagnose dyspepsia. In clinical practice, the ^{13}C GE test is commonly performed using an egg sandwich. Knight et al.[23] showed that something as seemingly insignificant as the cooking method of the egg may already influence tracer behavior. It should therefore be strongly advised to look further into the validity of current clinical practice using BT to diagnose abnormal GE.

4.1 | Limitations

Measurement of GE with a conventional MRI scanner requires participants to be in a supine position. We observed differences between our treatments, however, this supine position means that gastric content flows slower through the pyloric sphincter, due to gravity not propagating flow as effectively as it would in a standing or sitting position. The observed emptying may therefore be slower than in a more natural position, but relative differences should remain intact.

The current study assessed GE over 90 minutes with both BT and MRI, whereas other studies kept collecting breath samples after finishing the MRI measurements.[10,11] Our MRI measurements showed that at the end of the sampling time not all of the meal had emptied from the stomach. For research in which relative GE rates between groups are compared, gathering breath samples for 90 minutes can be sensitive enough to measure different emptying rates as these differences occur already quickly after ingestion.

For this study, we chose to include only male participants in order to maintain a homogenous group. Moreover, isotope measurements for short periods such as 90 minutes are not standard procedure and this relatively short duration may have influenced our results. However, we have a relatively large dataset of 60 GE events of both techniques simultaneously, which allows within subject rankings of both techniques. When we look at individual data large discrepancies can be seen between the ranking based on BT and that based on MRI. The rankings are very different in up to 40% of participants. In our opinion, this can not only be the result of our relatively short sample gathering time.

4.2 | The challenges of indirect measurement methods

GE measurements with the indirect BT method have been used in many different studies.[15,19,24-26] Nevertheless, there has been discussion on the validity of indirect measurements and the GE times which are inferred from them.[27-30] BT results are based on the solubility, bio-availability, absorption, metabolization, and excretion of the used tracer. To guarantee reliable study results it is important that the tracer is distributed evenly throughout the food stimulus that it is bio-available, directly absorbed by the intestine, and

metabolized by the liver upon availability. A likely explanation for discrepancies between direct and tracer-based methods is that the behavior of the tracer and its interaction with the intestine and liver is influenced by the food matrix in which it is delivered.

In addition, different tracer compounds have different chemical properties. It has been suggested that ^{13}C acetate might lead to higher ^{13}C levels within the CO_2 in breath more quickly than octanoic acid due to faster metabolism of acetate.[31] This would make ^{13}C acetate a better tracer for short duration trials, however, acetate has a large affinity for water. ^{13}C octanoic acid is a lipophilic compound and has been used in experiments with both liquid and solid test foods.[1,32] We used octanoic acid as a tracer because of the fat component of the meals. Octanoic acid has affinity for fatty foods.[33] With fat containing foods intragastric lipid layering can occur.[34,35] Intragastric lipid layering is of concern as experimental foods may contain a fat component. This fat component can affect tracer distribution and may influence measurement results. When layer formation occurs within the stomach, labeling techniques are inherently unreliable; The label will move with either the water, fat, or sediment phase (dependent on the chosen molecule) and thus either over- or underestimate the actual emptying rate. In our data, there is no evidence of intragastric layering within the measurement period.

Very recent evidence for this effect of gastric lipid content on tracers has been reported by Parker et al.[11] This study used acid stable and unstable stimuli, and compared three differed tracing agents (including acetate and octanoic acid) with MRI measurements to assess whether the distribution of tracing agents was influenced by the food matrix. Their results show that octanoic acid measurements correlate better with fat movement through the stomach than acetate and ^{13}C trioctanoin measurements, indicating that the chemical properties of the tracer may have influenced GE.

Such food matrix effects may have resulted in over- or underestimation in previous tracer-based work. The food stimuli we used contained all macronutrients of a normal meal in relative percentages. The rationale for this was to find results valid for actual meals and also to exclude specific macronutrient effects.[34,36-38] However, using regular foods makes the tracer choice challenging, because intragastric tracer behavior becomes less predictable as the food matrix becomes more complex. A possible solution would be to combine multiple tracers or use a combination of a radioactive marker and a tracer. However, also in that case prior validation is required to ascertain that the labeling works as intended.

5 | CONCLUSION

MRI and ^{13}C BT shows agreement on the group level; with a relatively short time of data collection (90 minutes), we were able to establish similar differences in GE between four foods for both methods. In contrast, on the individual level our results show over- or underestimations of half emptying times depending on the curve fitting method used and different ranked GE times between treatments.

In contrast with BT, MRI does not depend on tracer binding and recovery. Therefore, we advise researchers and clinicians to validate their BT-protocol for each type of food stimulus with MRI before using it as a measure of GE time.

DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

GC, MM, BW, CdG, and PS designed the study. GC did the data acquisition, analyses, and wrote the manuscript. MM, BW, CdG, and PS revised the manuscript. All authors have approved the manuscript.

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REFERENCES

1. Ritz MA, Fraser R, Edwards N, et al. Delayed gastric emptying in ventilated critically ill patients: measurement by 13C-octanoic acid breath test. *Crit Care Med*. 2001;29:1744-1749.
2. Wijlens AG, Erkner A, Mars M, de Graaf C. Longer oral exposure with modified sham feeding does not slow down gastric emptying of low- and high-energy-dense gastric loads in healthy young men. *J Nutr*. 2015;145:365-371.
3. Zhu Y, Hsu WH, Hollis JH. The impact of food viscosity on eating rate, subjective appetite, glycemic response and gastric emptying rate. *PLoS ONE*. 2013;8:e67482.
4. Schmidt PT, Abrahamsson H, Dolk A, et al. Methods to assess gastric motility and sensation. *Scand J Gastroenterol*. 2008;43:1285-1295.
5. Schwizer W, Steingoetter A, Fox M. Magnetic resonance imaging for the assessment of gastrointestinal function. *Scand J Gastroenterol*. 2006;41:1245-1260.
6. Elashoff JD, Reedy TJ, Meyer JH. Analysis of gastric emptying data. *Gastroenterology*. 1982;83:1306-1312.
7. Fruehauf H, Menne D, Kwiatek MA, et al. Inter-observer reproducibility and analysis of gastric volume measurements and gastric emptying assessed with magnetic resonance imaging. *Neurogastroenterol Motil*. 2011;23:854-861.
8. Glerup H, Bluhme H, Villadsen GE, Rasmussen K, Ejskjaer N, Dahlerup JF. Gastric emptying: a comparison of three methods. *Scand J Gastroenterol*. 2007;42:1182-1186.
9. Sanaka M, Nakada K. Stable isotope breath tests for assessing gastric emptying: a comprehensive review. *J Smooth Muscle Res*. 2010;46:267-280.
10. Bluemel S, Menne D, Fried M, Schwizer W, Steingoetter A. On the validity of the 13C-acetate breath test for comparing gastric emptying of different liquid test meals: a validation study using magnetic resonance imaging. *Neurogastroenterol Motil*. 2015;27:1487-1494.

11. Parker HL, Liu D, Curcic J, et al. Gastric and postgastric processing of 13C markers renders the 13C breath test an inappropriate measurement method for the gastric emptying of lipid emulsions in healthy adults. *J Nutr*. 2017;147:1258-1266.
12. Sanaka M, Urita Y, Sugimoto M, Yamamoto T, Kuyama Y. Comparison between gastric scintigraphy and the [13C]-acetate breath test with Wagner-Nelson analysis in humans. *Clin Exp Pharmacol Physiol*. 2006;33:1239-1243.
13. Marciani L, Gowland PA, Spiller RC, et al. Gastric response to increased meal viscosity assessed by echo-planar magnetic resonance imaging in humans. *J Nutr*. 2000;130:122-127.
14. Camps G, Mars M, De Graaf C, Smeets PAM. Empty calories and phantom fullness: a randomized trial studying the relative effects of energy density and viscosity on gastric emptying determined by MRI and satiety. *Am J Clin Nutr*. 2016;104:73-80.
15. Ghoos YF, Maes BD, Geypens BJ, et al. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. *Gastroenterology*. 1993;104:1640-1647.
16. Maes BD, Ghoos YF, Geypens BJ, et al. Combined carbon-13-glycine/carbon-14-octanoic acid breath test to monitor gastric emptying rates of liquids and solids. *J Nucl Med*. 1994;35:824-831.
17. Maes BD, Geypens BJ, Ghoos YF, Hiele MI, Rutgeerts PJ. 13C-octanoic acid breath test for gastric emptying rate of solids. *Gastroenterology*. 1998;114:856-857.
18. Bluck LJC, Coward WA. Measurement of gastric emptying by the 13C-octanoate breath test - rationalization with scintigraphy. *Physiol Meas*. 2006;27:279-289.
19. Braden B, Adams S, Duan L-P, et al. The [13C]acetate breath test accurately reflects gastric emptying of liquids in both liquid and semisolid test meals. *Gastroenterology*. 1995;108:1048-1055.
20. Sanaka M, Yamamoto T, Ishii T, Kuyama Y. The Wagner-Nelson method can generate an accurate gastric emptying flow curve from CO2 data obtained by a 13C-labeled substrate breath test. *Digestion*. 2004;69:71-78.
21. Sanaka M, Nakada K, Nosaka C, Kuyama Y. The Wagner-Nelson method makes the [13C]-breath test comparable to radioscintigraphy in measuring gastric emptying of a solid/liquid mixed meal in humans. *Clin Exp Pharmacol Physiol*. 2007;34:641-644.
22. Bluck LJC. Recent advances in the interpretation of the 13C octanoate breath test for gastric emptying. *J Breath Res*. 2009;3:034002.
23. Knight LC, Kantor S, Doma S, Parkman HP, Maurer AH. Egg labeling methods for gastric emptying scintigraphy are not equivalent in producing a stable solid meal. *J Nucl Med*. 2007;48:1897-1900.
24. Raychaudhuri A, Shu V, Verlinden M. An alternative model for the estimation of gastric half emptying time (T50) of a solid meal using the 13C-octanoic acid breath test. *Gastroenterology*. 1998;114:A826.
25. Cappello G, Malatesta MG, Ferri A, et al. Gastric emptying of a solid-liquid meal measured with 13C octanoic acid breath test and real-time ultrasonography: a comparative study. *Am J Gastroenterol*. 2000;95:3097-3100.
26. Delbende B, Perri F, Couturier O, et al. 13C-octanoic acid breath test for gastric emptying measurement. *Eur J Gastro Hepatol*. 2000;12:85-91.
27. Choi MG, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA, Nair KS. [13C]octanoic acid breath test for gastric emptying of solids: accuracy, reproducibility, and comparison with scintigraphy. *Gastroenterology*. 1997;112:1155-1162.
28. Choi MG, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA, Nair KS. Reproducibility and simplification of 13C-octanoic acid breath test for gastric emptying of solids. *Am J Gastroenterol*. 1998;93:92-98.
29. Perri F, Clemente R, Festa V, Andriulli A. 13C-octanoic acid breath test: valueless test for gastric emptying? *Gastroenterology*. 1998;114:857-858.
30. Sanaka M, Yamamoto T, Kuyama Y. Theoretical flaws in the gastric emptying breath test: why is it dubious? *Dig Dis Sci*. 2005;50:15-17.
31. Sanaka M, Yamamoto T, Kuyama Y. Retention, fixation, and loss of the [13C] label: a review for the understanding of gastric emptying breath tests. *Dig Dis Sci*. 2008;53:1747-1756.
32. Chew CG, Bartholomeusz FDL, Bellon M, Chatterton BE. Simultaneous 13C/14C dual isotope breath test measurement of gastric emptying of solid and liquid in normal subjects and patients: comparison with scintigraphy. *Nucl Med Rev*. 2003;6:29-33.
33. Verbeke K. Will the 13C-octanoic acid breath test ever replace scintigraphy as the gold standard to assess gastric emptying? *Neurogastroenterol Motil*. 2009;21:1013-1016.
34. Mackie AR, Rafiee H, Malcolm P, Salt L, van Aken G. Specific food structures supress appetite through reduced gastric emptying rate. *Am J Physiol Gastrointest Liver Physiol*. 2013;304:G1038-G1043.
35. Camps G, Mars M, de Graaf C, Smeets PAM. A tale of gastric layering and sieving: gastric emptying of a liquid meal with water blended in or consumed separately. *Physiol Behav*. 2016;176:26-30.
36. Moran TH, McHugh PR. Distinctions among three sugars in their effects on gastric emptying and satiety. *Am J Physiol*. 1981;241:R25-R30.
37. Shin HS, Ingram JR, McGill AT, Poppitt SD. Lipids, CHOs, proteins: can all macronutrients put a 'brake' on eating? *Physiol Behav*. 2013;120:114-123.
38. Hillyard S, Cowman S, Ramasundaram R, Seed PT, O'Sullivan G. Does adding milk to tea delay gastric emptying? *Br J Anaesth*. 2014;112:66-71.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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