Title:

Gastric accumulation of enteral nutrition reduces pressure changes induced by phasic contractility in an isovolumetric intragastric balloon.

Running title:

Gastric content volume and contractility

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27 **Abstract**

28 **Background:** An isovolumetric intragastric balloon to continuously measure gastric phasic contractility
29 was recently developed by us. We aimed to investigate the readout of this technique in relation to
30 gastric content and gastric emptying.

31 **Methods:** In this crossover investigation the VIPUN™ Gastric Monitoring System, which comprises a
32 double lumen nasogastric feeding tube with integrated intragastric balloon, was used to assess phasic
33 gastric contractility by interpretation of the pressure in an isovolumetric balloon in 10 healthy subjects.
34 Balloon pressure was recorded in fasted state, during a 2-hour intragastric nutrient infusion (1 $kcal.ml^{-1}$
35 at 25, 75 or 250 $ml.h^{-1}$) and 4 hours post-infusion, and quantified as Gastric Balloon Motility Index
36 (GBMI), ranging from 0 (no contractility) to 1 (maximal contractility). Gastric accumulation was
37 quantified with magnetic resonance imaging and gastric emptying with a ^{13}C-breath test. Results are
38 expressed as mean(SD).

39 **Key Results:** GBMI was significantly lower during infusion at 250 $ml.h^{-1}$ compared to baseline
40 (0.13(0.05) versus 0.46(0.12)) and compared to infusion at 25 (0.54(0.21)) and 75 $ml.h^{-1}$ (0.43(0.20)),
41 all P<.005. Gastric content volume was larger after infusion at 250 versus 75 $ml.h^{-1}$ (P<.001). Half-
42 emptying time and accumulation were both negatively correlated with postprandial contractility.
43 Postprandial GBMI was significantly lower when GCV>0 ml compared to when the stomach was empty.

Conclusions & Inferences: Enteral nutrition dose-dependently decreased the contractility readout. This decrease was linked to gastric accumulation of enteral nutrition.

Key words

Enteral nutrition, medical device, gastric motility, gastric content volume, gastric emptying

Introduction

When the stomach is empty, gastric motility is characterized by the cyclic phasic contractility pattern of the migrating motor complex. Nutrient intake initially results in a tonic relaxation of the stomach and interruption of the migrating motor complex.[1-3] In general a fed motor pattern emerges upon intake of approximately 250 kcal[4] and increasing nutrient exposure augments the extent and duration of this initial inhibitory motor effect.[5-7] In a later stage, phasic contractions mix and grind the meal into smaller particles that can be emptied into the duodenum.[8]

Gastric emptying of a meal into the duodenum depends on propulsive tonic and phasic contractility of the stomach in combination with the opening and closure of the pyloric sphincter.[9] In the early phase of gastric emptying, a sample of the ingested meal is emptied quickly to the duodenum.[5,10] Nutrient sensing by duodenal receptors activates a neurohumoral duodeno-gastric feedback loop.[6,11] One of the functions of this feedback is to modulate gastric motility in order to limit the speed of gastric outflow. Ideally, gastric outflow does not exceed the processing and absorptive capacity of the small intestine. The magnitude of gastric emptying inhibition following duodenal nutrient exposure is dose- and composition-dependent.[5,6,11-13] These mechanisms are implicated for liquid, mixed and solid meals.[9,10,14] Moreover, solid meals require trituration prior to passage through the pylorus.[15]

Understanding the relationship between nutrient load, gastric motility and emptying is especially important when (unconscious) patients are fed liquid nutrients via a nasogastric tube, i.e. enteral nutrition, as is the case in critical care.[16] Enteral nutrition (1-2 $kcal.ml^{-1}$) is typically provided at infusion rates starting at 10 - 20 $ml.h^{-1}$ and increased up to 150 $ml.h^{-1}$ or 30 $kcal.kg^{-1}.day^{-1}$.[17,18] An important risk of enteral nutrition is intolerance to the nutrients which might result in vomiting and potentially life-threatening complications.[19] Intolerance to enteral nutrition is often blamed on impaired motility and emptying, although these aspects are not easily monitored in clinical practice.[20-22] Current practice at the intensive care unit is to aspirate and quantify gastric residual volume manually. The value and accuracy of gastric residual volume aspiration has been widely disputed and support from guidelines

is diminishing.[16,23-25] Nevertheless, the technique remains widely used due to a lack of practical alternatives. In research settings, manometry and barostat investigations can be used to assess gastric motility in detail.[26] However, these techniques are not suited for daily clinical use at an intensive care unit. Similarly, none of the existing gastric emptying tests, such as scintigraphy, tracer tests and imaging techniques are feasible bedside tools to routinely evaluate gastric emptying rate of critically ill patients.[27]

The VIPUN™ Gastric Monitoring System (GMS) is a novel medical device developed at KU Leuven that enables to measure stomach contractility by means of a nasogastric balloon catheter.[2] This bedside tool allows to continuously assess phasic gastric contractility while liquid nutrients can be infused intragastrically through the same catheter. In order to assess the impact of enteral nutrition on the system's readout, we set out to measure the gastric motor response with this new device in response to gastric filling with enteral nutrition, infused at three infusion rates, while simultaneously quantifying gastric accumulation and half-emptying time. The infusion rates mimic feeding in clinical practice and relative overprovision. We hypothesized that relative under- and overfeeding results in substantially different contractility readouts in healthy subjects via activation of the feedback mechanism.

Materials and methods

Study design

This was a single-center three-way crossover investigation with an investigational medical device in healthy adults. Healthy men and women with a BMI between 18 and 30 were recruited. The main exclusion criteria were chronic dyspeptic symptoms assessed with the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index questionnaire, gastrointestinal disorders, psychological or psychiatric disorders, pregnancy, lactation, contra-indications for the placement of a nasogastric feeding tube, contra-indications for magnetic resonance imaging (MRI) such as claustrophobia or metal implants, and use of drugs with the exclusion of contraception. Written

informed consent was obtained prior to any study-specific procedures. Enrolment and study procedures took place from October 3, 2018 until April 3, 2019. The investigation was approved by the ethics committee of UZ/KU Leuven (reference: S61853), registered on clinicaltrials.gov (NCT03664570) and was performed in accordance with the Declaration of Helsinki.

Investigational medical device

The VIPUN™ Gastric Monitoring System (GMS) was used to measure gastric contractility. This technique was previously validated in healthy subjects.[2] The investigational medical device under development comprises of a single-use 12 French double lumen nasogastric catheter (Vygon, Ecouen, France) on which a polyurethane balloon (Via Biomedical, Maple Grove, MN, USA) was mounted. The deflated balloon catheter can be passed through the nose. Once in the stomach the balloon was manually inflated with 150 ml air.

Intra-balloon pressure fluctuations were measured with a custom-made extracorporeal control unit. The control unit consisted of a pressure sensor (MPX2050DP, NXP Freescale™, Munich, Germany) and data acquisition unit (DI-245, DATAQ™Instruments, Akron, OH, USA) that was connected to a personal computer (Dell Latitude™ E5540, Round Rock, TX, USA). Pressure was recorded at 5 Hz with a resolution of 0.1 mmHg (WinDaq™ data acquisition software, DATAQ™ Instruments, Akron, OH, USA). The balloon catheter was designed to allow intragastric infusion of liquids while simultaneously recording intraballoon pressure.

Study procedures

The investigation comprised a screening visit to assess subject eligibility and three study visits with different infusion rates of enteral nutrition (25, 75 and 250 $ml.h^{-1}$). Each subject was randomly assigned to a treatment order upon enrolment. During each study visit, intraballoon pressure was recorded with the GMS for 8 hours, 2 hours in fasted state, 2 hours during nutrient infusion and 4 hours after

cessation of infusion. A ^{13}C-octanoate breath test for gastric emptying was performed. Enteral formula (Isosource® Standard, 100 kcal, 3.9 g proteins, 13.5 g carbohydrates and 3.4 g lipids per 100 ml; Nestlé Health Science, Brussels, Belgium) was supplemented with 1-^{13}C sodium-octanoate (Cambridge Isotope Laboratories, Tewksbury, MA, USA) to a final concentration of 0.5 mg.ml^{-1}. The enriched enteral formula was infused intragastrically via the widest lumen of the balloon catheter over a period of 2 hours at 25, 75 or 250 ml.h^{-1} depending on the condition. Breath samples were collected by exhaling through a straw in 12 ml glass Exetainers® (Labco, Lampeter, Wales). Two baseline samples were collected prior to infusion and subsequently samples were collected every 15 minutes up to 6 hours in total. Gastric emptying through the pylorus, followed by small intestinal absorption, is the rate-limiting step of $^{13}CO_2$ appearance in exhaled breath.[28]

MRI was performed to determine total gastric content volume (GCV = volume of liquid meal and gastric secretions) at 9 time points throughout each visit with infusion rate 75 or 250 ml.h^{-1}, not at 25 ml.h^{-1}. A 1.5T MRI system (Philips, Best, The Netherlands) with an abdominal, four-channel phased-array receive coil was used. T1 weighted fast spin echo sequences with 4 mm slice thickness in the transverse and coronal plane as well as a breath-hold T1 gradient-echo with 3 mm slice thickness in the transverse plane were used. The balloon catheter was disconnected during each MRI session without loss of balloon volume or pressure.

Hunger, satiation, bloating, nausea and epigastric discomfort/pain was scored on 100 mm visual analog scales (VAS, 0 mm = absent, 50 mm = pain threshold, 100 mm = worst possible sensation) prior to each MRI scan session.

Analysis

Intraballoon pressure fluctuations were analyzed offline by means of a custom-made algorithm designed in MatLab (MatLab® R2018a, The MathWorks®, Natick, MA, USA) by KU Leuven (Leuven, Belgium). Preprocessing of the pressure signal included the application of an interpolation filter to

remove high-amplitude artefacts and a low pass filter to discard high-frequency contractions (> 0.1 Hz). Gastric contractility-induced pressure waves were detected by means of the *findpeaks* function in MatLab. Gastric contractile waves were identified based on the following requirements: minimum inter-peak distance of 17 seconds, minimum peak base width of 17 seconds and a minimum half-prominence width of 7 seconds. Data were summarized as a gastric balloon motility index (GBMI) as published previously.[2] A single GBMI value was calculated per minute. GBMI represents the fraction of time during which gastric contractions were detected, hence ranging from 0 (no contraction in 60 seconds) to 1 (contractions continuously present). For the analysis, GBMI was summarized as the following endpoints of interest: $GBMI_{Fasted}$ for the baseline period in fasting state, $GBMI_{During}$ for the period during nutrient infusion (t = 120-240 min), $GBMI_{Early}$ for the early postprandial period (t = 241-360 min), $GBMI_{Late}$ for the late postprandial period (t = 361-480 min) and $GBMI_{Fed}$ that covers the entire fed state (t = 120 – 480 min).

Gastric emptying (GE) rate was expressed as gastric half-emptying time (GET½ [min]) as described previously.[2]

GCV (= meal volume + gastric secretions volume [ml]) was semi-automatically segmented by means of custom-designed image analysis software (Intellispace portal Discovery, Philips, Best, The Netherlands). Area under the GCV-curve, maximum GCV (GCV_{max}) and absolute GCV values at different time points were calculated.

Results are presented as mean (standard deviation). Normality of continuous data and residuals was assessed with Kolmogorov-Smirnov test and visual interpretation of histograms and QQ-plots.

Mixed models were applied with condition, period (fasted, during, early postprandial and late postprandial) and their interaction (if applicable) as fixed effects, taking into account the repeated measures obtained in the crossover study design. Bonferroni and Bonferroni-Holm corrections for multiple testing were applied. Associations were investigated with Spearman's correlation and simple linear regression. ANOVA with Tukey's multiple comparisons test was used for explorative analysis.

Gastric contractility, GE and GCV were analyzed for the per protocol population. Safety-related endpoints and epigastric symptoms were analyzed for the safety population.

Results

Study population

In total 19 subjects were enrolled in the study. The per protocol population consisted of a subset of 10 subjects with sufficiently complete data for full analysis and are reported here. Subject disposition and reasons for exclusion are shown in Figure 1. Four subjects tolerated the procedures poorly and withdrew consent, two other subjects withdrew consent due to a lack of time to continue participation. The per protocol population consisted of eight women and two men with a mean age of 33 (14) years and mean BMI of 24.1 (2.0) $kg.m^{-2}$.

Gastric contractility

$GBMI_{Fasted}$ was similar in all conditions (p = .777, Figure 2 and Figure 3). GBMI during nutrient infusion was significantly lower upon infusion at 250 $ml.h^{-1}$ (mean GBMI = 0.13 (0.05)) compared to 25 $ml.h^{-1}$ (0.54 (0.21), adjusted P < .001) and 75 $ml.h^{-1}$ (0.43 (0.20), adjusted P < .001). $GBMI_{During}$ was similar at 25 and 75 $ml.h^{-1}$ (adjusted P = 1).

Following infusion at 250 $ml.h^{-1}$, $GBMI_{Early}$ remained significantly lower compared to the other infusion rates (both adjusted P < .01). $GBMI_{Late}$ recovered towards baseline values in the late postprandial period, when there were no longer significant interaction effects between conditions (P = .056).

194 The nutrient-induced change in GBMI ($GBMI_{During} - GBMI_{Fasted}$) was different across conditions (P = .005,
195 Figure 4). The drop in GBMI was significantly greater when nutrients were infused at 250 $ml.h^{-1}$ (-0.33
196 (0.14)) compared to 25 $ml.h^{-1}$ (0.03 (0.25), P = .016) or 75 $ml.h^{-1}$ (-0.05 (0.15), P = .006).

197

198 Gastric emptying

199 GET½ was significantly longer when nutrients were infused at 250 $ml.h^{-1}$ compared to 75 $ml.h^{-1}$
200 (adjusted P = .003) and compared to 25 $ml.h^{-1}$ (adjusted P = .019, mixed models with Bonferroni-Holm
201 correction, Figure 5).

202 After 6 hours, a mean of 52.4 (8.9), 56.5 (4.0) and 46.6 (4.5)% of the administered ^{13}C dose was
203 recovered after infusion of 50, 150 and 500 ml respectively, with the cumulative dose recovered being
204 significantly lower in the latter condition as compared to the other conditions (both adjusted P < .001,
205 one-way repeated measures ANOVA with Tukey's multiple comparisons test).

206

207 Gastric content volume

208 Gastric content volume increased during nutrient administration, to reach a maximum at t = 210 min
209 (Figure 6). GCV values and derived parameters were not normally distributed in the 75 $ml.h^{-1}$ condition.
210 Median GCV at t = 240 min, GCV_{max} and AUC-GCV were significantly higher in the 250 $ml.h^{-1}$ condition
211 compared to 75 $ml.h^{-1}$ (all p-values < 0.0001, Wilcoxon matched-paired signed rank tests).

212 MRI images revealed post hoc that the distal tip of the catheter was positioned postpylorically in two
213 subjects (subject 7 and subject 10, both in the 75 $ml.h^{-1}$ condition). GET½ was indeed relatively short
214 in these cases (both 156.9 min, Figure 5 (right panel)). Data from these 2 subjects were consequently
215 omitted from the per protocol analysis.

216

217 Correlation analysis

GBMI in the early postprandial period and in the fed state in general were both significantly and negatively correlated with GET½ and GCV at t = 240 min in the pooled conditions (Table 1, Figure 7 panels A and B). Breath test-derived GET½ and MRI-derived parameters of gastric retention were significantly and positively correlated (Figure 7, panel C). When GCV was present in the stomach (GCV > 0 ml), contractility was lower as compared to when the stomach was empty (GBMI 0.29 (0.05) vs. 0.54 (0.04), P < .001, mixed model).

Safety

Nine adverse events were reported: headache (mild: n=1, moderate: n=2), moderate upper abdominal bloating (n = 2), vomiting (n = 1), mild epigastric discomfort (n = 1), mild epistaxis (n = 1) and mild pharyngeal pain (n = 1). Four subjects withdrew consent due to intolerance to the study procedures and/or the nasogastric tube.

Discussion

This was a monocenter, three-way cross-over pilot investigation in healthy adults. The aim was to establish the effect of gastric filling with enteral nutrition on gastric contractility as measured with the VIPUN GMS. It was hypothesized that the GMS should be able to differentiate the dose-dependent effects of nutrients on gastric phasic contractility. The relations between the contractility measurement, gastric half-emptying time and accumulation were investigated as well. Gastric half-emptying time and gastric content volume were quantified by a ^{13}C-octanoate breath test and MRI, respectively. Using the investigational medical device, we found that enteral nutrition dose-dependently decreased phasic contractility, which was associated with gastric accumulation and longer half-emptying times.

The dose-dependent decrease of phasic and tonic contractility in response to the nutrient stimuli is well established.[5,6,10,29] The investigational medical device is being developed as a monitor of phasic

gastric contractility for wide clinical use. We previously demonstrated that the device can differentiate normal and pharmacologically impaired contractility[2], as well as pharmacologically enhanced contractility.[30] The device was primarily developed to be used in daily clinical practice to monitor gastric motor function in patients requiring enteral nutrition, such as at the intensive care unit. A pilot study in this target population was conducted.[31] Infusion rates of 25 and 75 $ml.h^{-1}$ are often used in clinical practice, whereas 250 $ml.h^{-1}$ represents relative overprovision. Such a high infusion rate is not used in clinic, however we chose this rate to mimic relative overfeeding in healthy subjects with limited risk for discomfort. It is known that nutrient sensing is augmented in critically ill patients, which is considered a putative mechanism in the genesis of enteral feeding intolerance.[22] The current observations in healthy subjects support the hypothesis that relative overfeeding in critically ill patients leads to reduction of GBMI. This effect might even be enhanced in those patients with increased sensitivity to duodenal nutrients. Both aspects require confirmatory studies.

Gastric filling is associated with inhibition of motility and vice versa. On the other hand, larger meal volumes are known promote the absolute rate of gastric emptying.[10,32] Our observations of a transient reduction in GBMI upon nutrient intake are in agreement with the literature describing the transient gastric accommodation reflex.[33,34] It has been shown that duodenal glucose infusion inhibits antral wave frequency and enhances pyloric tone in a dose-dependent fashion.[35] Alternatively, also gastric distension could cause inhibition of antral contractility.[36]

As expected, gastric accumulation of the meal, measured with MRI was significantly more pronounced following infusion at 250 $ml.h^{-1}$ compared to 75 $ml.h^{-1}$. [5,37] Moreover, when nutrients were present in the stomach, GBMI was significantly lower as compared to when the stomach was empty. It is important to note that MRI revealed that nutrients occupied the distal and proximal stomach, and hence the balloon typically migrated towards the more compliant proximal stomach. Consequently, it is also likely that the balloon could not detect phasic contractions occurring at the distal stomach. Furthermore it can also not be excluded that fluids around the balloon induce a mechanical dampening

effect reducing the GBMI as such. Hence, the observed relation between accumulation and a reduction in GBMI might also be the net effect of three mechanisms at play: the physiologic feedback loop, displacement of the balloon away from the contractile events and a dampening effect of the surrounding fluids. The contribution of each mechanism should be elucidated, for instance by means of dynamic MRI. Regardless of the underlying mechanism, a prolonged reduction of the motility readout can provide valuable information for the nutritional strategy. To date, research tools to evaluate gastric motility and emptying rate in detail cannot be widely implemented in daily clinical practice. Once fully developed, the single use balloon catheter has the potential to provide an affordable, practical and reliable stand-alone solution to evaluate gastric function by means of a nasogastric feeding tube. The nature of the observed adverse events is similar to the use of manometry or barostat catheters. The clinical benefit remains to be evaluated in relevant patient populations.

As anticipated, GET½ was significantly longer with the highest infusion speed.[5,38] MRI confirmed this observation. Absolute ^{13}C-label recovery was different between conditions, although the concentration of administered ^{13}C-label was constant across conditions. Hence both the volume of nutrients emptied at the end of the experiment as well as the half-emptying time differed between the conditions. No validated thresholds have been defined for clinically relevant delayed GET½ for the applied test protocol with continuous infusion of a liquid meal. Besides phasic peristaltic contractions, also tonic contractions substantially contribute to gastric emptying.[9] Tonic and, probably to a lesser extent, phasic contractions contribute to an antroduodenal pressure gradient. This pressure gradient facilitates the flow of chyme through an intermittently opening pylorus.[9] The balloon dimensions and analysis method were developed specifically to focus on phasic contractility. Consequently, we could not address the contribution of tonic activity to gastric emptying in this investigation.

In those cases where gastric GBMI was unaffected by nutrient infusion, no elongation of gastric half-emptying time was expected. This was confirmed by the negative correlation between half-emptying time and GBMI. Even though we found a monotonic relation between half-emptying time and GBMI,

292 our data (see Figure 7, panel A) also suggest a more complex "L-shape" relation whereby the
293 half-emptying time is only prolonged when GBMI is relatively low. This observation is consistent with
294 our previous findings in healthy subjects (see Goelen *et al.* Figure 8)[2] and in critically ill patients (in
295 press).[31] Such relation should be addressed in future studies.

296 The breath test was selected due to its compatibility with MRI and the balloon measurement.[22] GCV-
297 derived parameters, measured with MRI were significantly correlated with GET½. However, both
298 techniques were not 100% in agreement (rho = 0.74). MRI should be considered the reference
299 technique in this comparison as it is the most direct readout of gastric retention, the inverse of gastric
300 emptying.[38-41] Breath tests are indirect semi-quantitative measures of gastric emptying, which rely on
301 multiple assumptions.[28,38,42] MRI is costly, time consuming and in high demand for clinical and research
302 use. Hence the consideration to not measure GCV when infusing nutrients at 25 $ml.h^{-1}$. This might be
303 perceived as a limitation, although in our experience infusion at such a low rate results in GCV values
304 close to zero (unpublished data). Based on the current observations with 75 $ml.h^{-1}$, this a priori
305 judgement seems justified. GCV remained below 10 ml at all time points in 8 out of 10 subjects when
306 enteral nutrition was infused at 75 $ml.h^{-1}$. The balloon catheter was disconnected for each scan session
307 in such a way that intraballoon volume was preserved. The monitoring system remained outside the
308 MRI room. Nutrients were infused postpylorically in two subjects. Both subjects were censored from
309 the statistical analysis. The tip of the nasogastric tube was positioned in the distal stomach in all other
310 cases.

311

312 Based on the observations made in this crossover investigation in healthy subjects, it was concluded
313 that the GMS readout was in agreement with the well-established dogma that nutrients dose-
314 dependently inhibit gastric contractility, which is also associated with gastric accumulation of nutrition
315 in the stomach. However, given that the reduction in contractility, as assessed with the GMS, was
316 closely correlated to antral accumulation of enteral nutrition it cannot be excluded that this reduction

was induced by the transient displacement of the balloon out of the distal stomach and/or a dampening effect of surrounding fluids.

The ^{13}C-octanoate breath test and MRI agreed with regard to gastric emptying rate. Gastric emptying, irrespective of the test methodology, was correlated with the contractility readout in the fed state as measured with the VIPUN GMS.

These data provide important insights for the further development of the VIPUN GMS as a clinical monitoring tool during enteral feeding.

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NG and PJ own shares in VIPUN Medical. All other authors have declared no conflicts of interest.

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Tables

444 **Table 1:** Correlation analysis of gastric half-emptying time (GET½), gastric content volume at the end
445 of infusion (t = 240 min, GCV_{240}) and Gastric Balloon Motility Index (GBMI) in different periods.
446 Spearman's rho and p-values are provided. Pooled conditions. GCV available for the infusion rates 75
447 and 250 $ml.h^{-1}$, number of observations (N Obs) = 20. GET½ available for all conditions (N Obs = 30).

		Spearman Correlation Coefficients					
	N Obs	$GBMI_{Fasted}$	$GBMI_{During}$	$GBMI_{Early}$	$GBMI_{Late}$	$GBMI_{Fed}$	GET½
GET½	30	-.04 .8309	-.22 .2398	-.51 .0037	.01 .9581	-.37 .0461	-
GCV_{240}	20	-.01 .9773	-.57 .0083	0.85 <.0001	-.20 .4087	-.62 .0035	.74 .0002

448

449

450 **Figure legends**

451 **Figure 1:** Subject disposition. All 19 screened subjects were enrolled and randomized, of which 12
452 completed all three conditions. Nutrients were infused postpylorically during two visits, excluding two
453 subjects from the per protocol population ICF: informed consent form.

454 **Figure 2:** Mean Gastric Balloon Motility Index (GBMI) over time is shown per condition in 30-minute
455 segments. Error bars show standard deviation Enteral nutrient (EN) infusion is indicated at t = 120-240
456 min. N = 10 per condition.

457 **Figure 3:** Boxplot of Gastric Balloon Motility Index (GBMI) per period and condition. Whiskers indicate
458 minimum and maximum observations. Mean values are connected between periods within each
459 condition. N = 10 per condition.

460 **Figure 4:** Nutrient-induced change in Gastric Balloon Motility Index (ΔGBMI) per condition. Mean and
461 standard deviation (SD) are shown.

Figure 5: Gastric emptying. Panel A: mean and standard deviation (SD) of gastric half-emptying time (GET½) per condition. Panel B: Absolute ^{13}C dose recovered over time per condition. Panel C: Cumulative ^{13}C dose recovered over time per condition. N = 10.

Figure 6: Gastric content volume over time as quantified by means of magnetic resonance imaging. Boxplot shows median, 25th and 75th percentile, whiskers show minimum and maximum that are not outliers. No outliers were observed. Mean values are connected. Per protocol population.

Figure 7: Relation between gastric contractility, emptying and accumulation. Panel A: relation between Gastric Balloon Motility Index (GBMI) in the fed state and gastric half-emptying time (GET½). Panel B: relation between GBMI in fed state and gastric content volume at t = 240 min. Panel C: Relation between breath test-derived GET½ and MRI-derived GCV at t = 240 min. Colors represent conditions. Spearman's correlation coefficient and p-values are provided. Simple linear regression line is shown.

Figures