The effect of macronutrients on gastric volume responses and gastric emptying in humans: a magnetic resonance imaging study

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The volume response of the stomach to meal ingestion, commonly referred to as gastric accommodation, consists of a relaxation of the proximal and distal stomach (23) enabling the accommodation of the meal volume load without a significant rise in pressure (2). Generally, the accommodation reflex is subdivided into two components: first, reflex or receptive relaxation almost instantaneously providing the required reservoir volume for the ingested meal, and second, an adaptive relaxation, which occurs after the initial gastric volume increase with further modulation of gastric tone, possibly by specific nutrients, and might contribute to the regulation of gastric emptying (12, 35). Although the accommodation response has been extensively studied in animals and humans, the factors controlling food-induced relaxation are still incompletely understood (12). The barostat technique, which is the accepted gold standard for measurement of gastric relaxation, detected different effects on gastric relaxation and on sensory responses following duodenal infusion of fat, protein, or mixed nutrients during sustained gastric distension (3, 17). However, this technique is invasive and uncomfortable, changes the intragastric distribution of a meal, and may exaggerate relaxation of the stomach wall by direct stimulation with the balloon (7, 13). In addition, it is not feasible to measure gastric emptying and gastric relaxation responses simultaneously (8).

Since gastric accommodation cannot be seen in isolation from gastric active (tone) and passive tissue properties, gastric motility and gastric emptying, the interaction between these motor events in the process of storage and emptying of a meal ideally should be assessed simultaneously with a single technique. Magnetic resonance imaging (MRI) allows measurement of gastric motility and emptying with high spatial and temporal resolution and has recently been proposed as a technique for the measurement of postprandial volumes of different regions of the stomach, with the objective of being able to assess postprandial gastric accommodation (35). MRI has been validated for measurement of gastric volumes, gastric emptying, and gastric contractile activity for liquid and solid meals (18, 24, 33) and provides data on both stomach and meal volumes. However, under noninvasive conditions using gastric volumetric imaging modalities, the relationship of the magnitude of the response to different macronutrient compositions of isocaloric meals is still unanswered (12).

Hence, the aim of this study was to measure simultaneously: 1) gastric volume responses (stomach and meal volumes) after ingestion of three meals of different macronutrient content, 2) the related gastric emptying, and 3) gastrointestinal perception in healthy volunteers.

Our hypothesis was that under noninvasive conditions changes in gastric tone induced by the three single isovolumic...
liquid meals of different macronutrient but of similar caloric content are indirectly reflected by an increase in gastric volume and induce comparable gastric volume and gastrointestinal sensory responses as shown in invasive studies using the gastric barostat technique. Since posture affects intragastric pressure and volume as measured by the barostat technique and can alter the dynamic of the emptying process as well as gastric motor activity (1, 6, 21, 22), all data on gastric volume responses and emptying were obtained by using an open-configuration MRI system that allowed the investigation of subjects in the seated body position.

METHODS

This prospective study was approved by the local Institutional Review Board, and informed consent was obtained from all volunteers. Parts of this study published in abstract form were mentioned in a recent review article (20, 34).

Subjects and Study Design

Twelve healthy normal-weight subjects [five men; age 19–42 yr (mean 31 yr); body mass index 22.2 ± 0.7 kg/m²] participated in this single-blinded prospective study.

None of the volunteers had gastrointestinal symptoms or a history of other diseases, drug allergies, or previous abdominal surgery (except appendectomy) nor was taking any drugs or supplements known to influence gastrointestinal motor function or nutrient metabolism or any regular medication apart from oral contraceptives. All subjects had a similar dietary history of the last 2 wk (11). Subjects were studied in seated body position after an overnight fast on three different morning sessions, separated by at least 1 wk. At each session they received one of the three isovolumic liquid meals of different macronutrient content and similar caloric content in randomized order. The 500-ml meal was continuously infused over 5 min at 100 ml/min by a nasogastric tube (Ch 12) by use of a perfusion pump. The infusion was started after an adaptation period of ~20 min to minimize gastrointestinal symptoms induced by the nasogastric tube. Before and during meal infusion none of the volunteers experienced abdominal discomfort or nausea.

Test Meals

The three test meals of 500 ml were 68.2 g/l soybean oil emulsion (Intralipid, Fresenius Kabi AG, Stans, Switzerland), 375 kcal, 308 mosm/l (referred to as fat); 200 g/l glucose solution, 400 kcal, 1,110 mosm/l (referred to as glucose), or 200 g/l albumin solution, 308 mosm/l (Albumin ZLB 20%, ZLB AG, Bern, Switzerland) referred to as protein).

Fat solution was derived by diluting original Intralipid 10% solution with water and 3.82 g/l NaCl. The emulsion comprised 52% linoleic acid, 22% oleic acid, 13% palmitic acid, 8% linolenic acid, 4% stearic acid, 1% other fatty acids, and 8.184 g/l egg phospholipids and 15 g/l glyc erin. To test acid stability, five 50-ml samples of fat solution were mixed with 1 M hydrochloric acid until a final pH of 1.5 was reached and then incubated under stirring for 8 ha t37°C. During the study period was subdivided into three phases: the infusion phase (t−t0), the early emptying phase (t0–t45), and the late emptying phase (t45–t90). Gastric relaxation (Ve relaxation) was defined as the volume difference between the initial stomach volume at t = 0 min postinfusion (V0) and the fasting stomach volume at t = −5 min (V fasting); initial meal emptying was defined as the difference of the volume at t = −5 min + 500 ml and the volume at t = 0 min. Stomach, meal, and intragastric air volumes were plotted over time to generate volume curves (Fig. 2). The area under the volume curves [AUC (l/min)] for the time intervals Δt = 0–15 min (AUCt0–15) and 0–45 min (AUCt0–45) were calculated using the trapezoid method.

To analyze the characteristics of the volume curves, the data were fitted to a three-parameter gastric emptying model. The model formula is given as V(t) = Vo(1+kt/τ)exp[−(t−τ)/τ], where Vo is an estimate of the volume postinfusion at t0 (ml) and t is the emptying time constant in minutes. The dimensionless positive parameter k models the lag phase; for k = 0, the formula reduces to exponential emptying. This model was recently introduced (19) to complement the power

A fast spoiled gradient echo sequence was used for imaging. Imaging parameters of the volume scan were 20 sagittal image planes (covering the total gastric region); repetition time, 170 ms; echo time, 7.5 ms; flip angle, 60°; field of view, 350 mm; slice thickness, 10 mm; interslice gap, 0 mm; matrix, 256 × 192 pixels; two breath holds of 22 s. A standard abdominal send-receive coil was used for excitation and image acquisition.

After localization of the stomach and visual control of the position of the nasogastric tube at t = −10 min, followed by imaging the preprandial stomach volume and gastric content volume at t = −5 min (V fasting), the test meal infusion was performed within the MRI system. Subsequently, starting at t = 0 min, MRI volume scans imaging the postprandial stomach and meal volumes were performed every 3 min until t = 15 min, then every 10 min until t = 45 min and every 15 min until t = 90 min after gastric infusion.

V fasting
exponential gastric emptying model for normalized volume data described by Elashoff et al. (16). The gastric emptying model can emulate an increase of the volume curve for $k > 1$, whereas the power exponential model is limited to monotonically decreasing emptying curves. 

**Gastrointestinal symptom scores.** The gastrointestinal symptom scores were grouped by time point of measurement (given as mean values) and were plotted against mean total stomach and meal volumes as described previously (27). Area under the symptom score curve over 90 min of the self-report scores was used to compare the effects of the different macronutrients on symptoms. Linear regression analysis was used to assess the relationship between symptom scores and gastric content.

Fig. 1. Seven exemplary of 12 sagittal magnetic resonance image planes (thickness 10 mm) covering the gastric region after ingestion of the 500-ml protein meal in 1 representative subject presented from left lateral (image 6) to right lateral (image 17) showing the segmented stomach volume. The corresponding 3-dimensional representation of the 12 calculated total stomach contours is displayed at bottom right. Note the clear contrast between intragastric meal and air volume within the segmented stomach volumes of the first images. SV, stomach volume; MV, intragastric meal volume.

Fig. 2. Volume curves for stomach (--; meal (--) volumes of 12 subjects and 3 isovolumic (500 ml) liquid meals (375–400 kcal) of different macronutrient content in seated body position. Lines were computed from the coefficients estimated in the overall fit to the gastric emptying model (dashed lines, stomach volumes; solid lines, meal volumes).
Gastric Volume Responses

Infusion phase (t₀−t₀), $V_{\text{fasting}}$ for stomach volume and gastric content between the treatment groups was not different (Table 1). After infusion, $V_{\text{0}}$ for meal and stomach was higher for glucose than for protein and fat ($P < 0.01$). $V_{\text{relaxation}}$ was highest for glucose with differences between glucose and protein or fat ($P < 0.01$; Table 1). Initial meal emptying was higher for fat and protein than for glucose (fat, $-37 ± 17$ ml and protein, $-42 ± 22$ ml vs. glucose $17 ± 22$ ml, $P < 0.05$). Postprandial intragastric air increased significantly (mean air increase, $57 ± 15$ ml; $P < 0.01$) with a similar volume for each macronutrient. $V_{\text{relaxation}}$ for the stomach was associated with intragastric air increase ($r = 0.67$, $P < 0.001$).

Gastric emptying phases. The stomach and meal volume curves of glucose and fat were characterized by a prominent early volume increase followed by a continuous gastric emptying pattern. For protein, this volume increase was negligible (Fig. 3). AUC₀⁻₁₅ and AUC₀⁻₄₅ were higher for glucose than for protein ($P < 0.01$; Fig. 3, Table 1). The early increase in meal and stomach volume, indicated by the coefficient $k$, was larger for fat than for glucose ($P < 0.05$) and protein ($P < 0.01$). For all test meals, the volume increases were similar for meal and stomach volume, reflected by similar $k$ values ($P = 0.37$) given in Table 1. During this time interval, intragastric air remained constant and was not different between the treatment groups ($P > 0.05$, data not shown). During the last 45 min (late emptying phase) of the measurement period, fat emptied faster than glucose and protein ($P < 0.001$; Table 1). Intragastric air volume remained constant (mean $A_{\text{fslope}}$ of emptying curve, $0.02$ ml/min) and similar for the treatment groups ($P > 0.05$, data not shown).

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### Table 1. Effects of 3 different macronutrients on gastric volume responses in 12 healthy volunteers in seated body position

<table>
<thead>
<tr>
<th></th>
<th>Meal</th>
<th>Stomach</th>
<th>Meal</th>
<th>Stomach</th>
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<tbody>
<tr>
<td>$V_{\text{fasting}}$</td>
<td>65 ± 22</td>
<td>178 ± 18</td>
<td>67 ± 22</td>
<td>180 ± 18</td>
</tr>
<tr>
<td>$V_{0}$</td>
<td>532 ± 27</td>
<td>696 ± 22</td>
<td>596 ± 27*</td>
<td>759 ± 22*</td>
</tr>
<tr>
<td>$V_{\text{relaxation}}$</td>
<td>460 ± 17</td>
<td>517 ± 14</td>
<td>525 ± 17*</td>
<td>581 ± 14*</td>
</tr>
<tr>
<td>$K$</td>
<td>1.34 ± 0.10‡</td>
<td>1.41 ± 0.08‡</td>
<td>1.14 ± 0.10</td>
<td>1.21 ± 0.08</td>
</tr>
<tr>
<td>$t_{\text{50}}$</td>
<td>87 ± 8§</td>
<td>104 ± 7§</td>
<td>126 ± 8</td>
<td>143 ± 7</td>
</tr>
<tr>
<td>AUC₀⁻₄₅min</td>
<td>8.4 ± 0.4</td>
<td>10.9 ± 0.4</td>
<td>9.1 ± 0.4†</td>
<td>11.6 ± 0.4†</td>
</tr>
<tr>
<td>AUC₀⁻₁₅min</td>
<td>23.9 ± 1.3</td>
<td>31.8 ± 1.1</td>
<td>26.1 ± 1.3</td>
<td>33.0 ± 1.1†</td>
</tr>
</tbody>
</table>

Values are means ± SE. AUC, area under curve; $V_{\text{relaxation}}$, gastric relaxation defined as $V_{0} - V_{\text{fasting}}$, where $V_{0}$ is stomach volume at 0 min postinfusion and $V_{\text{fasting}}$ is fasting stomach volume at 5 min before infusion; $k$, regression estimated coefficient for volume rise after $V_{0}$; $t_{\text{50}}$, half emptying time. *$P < 0.01$ vs. protein, fat; †$P < 0.01$ vs. protein; §$P < 0.05$ vs. protein, glucose; ‡$P < 0.001$ vs. protein, glucose. For all parameters, except for $k$, $P < 0.01$ for meal vs. stomach.

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### Statistical Analysis

Statistical descriptive calculations, calculations for linear regression analysis, and (Spearman) correlation analysis were performed using the data analysis package R (31). To stabilize parameter estimates ($V_{0}$, $k$, $t_{\text{empt}}$) of the model, these were not determined from individual curve fits but estimated from a single statistical fit to all volume data using the R library nlme (30). The half emptying time ($t_{\text{empt}}$) for stomach and meal volume was determined from the parameters $k$ and $t_{\text{empt}}$ by Newton approximation. Average volume curves for each meal and position were calculated. The slopes of individual intragastric air volume curves ($A_{\text{fslope}}$) were determined by linear regression analysis. Effects of macronutrients were compared using a mixed model ANOVA, with “subject” as a random variable and “treatment” and “meal/stomach” as fixed variables (30). Data were considered to be significant at $P < 0.05$. Bonferroni correction was applied for three pairwise comparisons of each macronutrient. Data are presented as means ± SE. The results presented in the tables are group mean averages calculated by ANOVA and thus differ slightly from the raw data presented in the figures.

### RESULTS

Image acquisition and analysis were performed successfully in all subjects. The image quality attained with the 0.5-T open-configuration MRI system allowed semiautomated detection and computation of stomach, meal, and intragastric air volumes.

Gastric Volume Responses

**Infusion phase** ($t_{0}−t_{0}$), $V_{\text{fasting}}$ for stomach volume and gastric content between the treatment groups was not different (Table 1). After infusion, $V_{0}$ for meal and stomach was higher for glucose than for protein and fat ($P < 0.01$). $V_{\text{relaxation}}$ was highest for glucose with differences between glucose and protein or fat ($P < 0.01$; Table 1). Initial meal emptying was higher for fat and protein than for glucose (fat, $-37 ± 17$ ml and protein, $-42 ± 22$ ml vs. glucose $17 ± 22$ ml, $P < 0.05$). Postprandial intragastric air increased significantly (mean air increase, $57 ± 15$ ml; $P < 0.01$) with a similar volume for each macronutrient. $V_{\text{relaxation}}$ for the stomach was associated with intragastric air increase ($r = 0.67$, $P < 0.001$).

**Gastric emptying phases.** The stomach and meal volume curves of glucose and fat were characterized by a prominent early volume increase followed by a continuous gastric emptying pattern. For protein, this volume increase was negligible (Fig. 3). AUC₀⁻₁₅ and AUC₀⁻₄₅ were higher for glucose than for protein ($P < 0.01$; Fig. 3, Table 1). The early increase in meal and stomach volume, indicated by the coefficient $k$, was larger for fat than for glucose ($P < 0.05$) and protein ($P < 0.01$). For all test meals, the volume increases were similar for meal and stomach volume, reflected by similar $k$ values ($P = 0.37$) given in Table 1. During this time interval, intragastric air remained constant and was not different between the treatment groups ($P > 0.05$, data not shown). During the last 45 min (late emptying phase) of the measurement period, fat emptied faster than glucose and protein ($P < 0.001$; Table 1). Intragastric air volume remained constant (mean $A_{\text{fslope}}$ of emptying curve, $0.02$ ml/min) and similar for the treatment groups ($P > 0.05$, data not shown).
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DISCUSSION

The present study shows for the first time the relationship between the magnitude of the gastric volume responses to ingestion of three single liquid meals of different macronutrient composition and their effect on gastrointestinal perception in healthy volunteers. The use of the open-configuration MRI system combined with an optimized analysis method for nutrient liquid gastric emptying allowed a simultaneous, noninvasive, and direct assessment of the actual postprandial meal (fluid) volume changes during the ingestion and early emptying phase. Whether the parameters are modulated by the higher caloric content or the higher osmolality of the glucose meal or the macronutrient itself remains unclear. The observed similar initial emptying and distribution process and thus largely prevents the averaging of important effects determining gastric accommodation. It is very likely that the lack of data on the actual meal volume changes during the ingestion and early emptying process generated those contradictory results in the study of van den Elzen et al. (39), e.g., by counterbalanced effects of an initial air increase and meal decrease, or by belching during ingestion.

Contrary to our hypothesis, initial meal volume and thus gastric relaxation was more pronounced after ingestion of glucose, resulting in higher gastric volumes immediately after ingestion. Glucose meal volume also remained elevated compared with fat and protein during the early emptying phase. Lower initial meal emptying and accumulation of secretion or swallowed saliva for the glucose meal can be responsible for this initial and persisting elevation (40). However, it must be considered that the glucose meal had a significant larger osmolality (1,110 mosm/l) compared with fat and protein (308 mosm/l), which presents an unfortunate pitfall of this study. Whether the parameters are modulated by the higher caloric content or the higher osmolality of the glucose meal or the macronutrient itself remains unclear. The observed similar

<table>
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<tr>
<th>Table 2. Sensory responses in 12 healthy volunteers after infusion of 3 different macronutrients</th>
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<tr>
<td>AUC&lt;sub&gt;0–90min&lt;/sub&gt; [min]</td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Fullness</td>
</tr>
<tr>
<td>Satiety</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Bloating</td>
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</table>

Values are means ± SE. AUC<sub>0–90min</sub> area under the symptom score curve over 90 min. *P < 0.01 vs. protein, glucose

Sensory Responses

There were no differences in sensory responses for fullness, satiety, and bloating between the test meals. Perception scores for nausea were higher for fat than for glucose or protein (P < 0.05) (Table 2). A significant linear trend was found for meal or stomach volume and the perception of fullness and satiety (Fig. 4). A weak association was observed between the perception of nausea and total meal and stomach volume (fat, R<sup>2</sup> = 0.50; glucose, R<sup>2</sup> = 0.42; protein, R<sup>2</sup> = 0.44; for all P < 0.05). No significant trend was found for bloating (data not shown).

Fig. 4. Association between mean meal volume and perception of fullness (A) and satiety (B) for the three different nutrient liquid meals (●, fat; ▲, glucose; ■, protein). A: R<sup>2</sup> = 0.98 for fat, R<sup>2</sup> = 0.85 for protein, and R<sup>2</sup> = 0.76 for glucose, P < 0.001. B: R<sup>2</sup> = 0.94 for fat, R<sup>2</sup> = 0.92 for protein, and R<sup>2</sup> = 0.92 for glucose, P < 0.001.

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meal emptying patterns during the early emptying phase for all meals with no differences in gastric half emptying time between the glucose and the protein meal indicate that the minor difference in caloric density seems to be negligible. The fast inhibitory influence on initial gastric emptying of glucose may be explained by activation of osmosensitive afferent fibers, which are known to respond with a short latency (<7 s) to hyperosmolar solutions (29). Despite these differences in initial gastric meal volumes, the corresponding intragastric air increases were similar irrespective of the macronutrient. This indicates that the initial relaxation of the stomach is determined mainly by the resulting gastric meal volume load. How intragastric air increase is caused and may contribute to or modulate this process (possibly by altering intragastric pressure by receptive accommodation) has to be clarified in further studies.

The volume increases during the early gastric emptying period had similar characteristics for meal and stomach volume for all test meals. The dynamics of intragastric air volumes were comparable for all macronutrient meals, confirming that, primarily, the ingested meal volume and, secondarily, its change by gastric secretion and emptying (as reflected by different k values of the gastric emptying model) were the major determinants of stomach volume response after intake of a caloric liquid meal. Several gastric barostat studies have shown that macronutrients affect gastric tone, with fat infused into the proximal intestine causing a rapid and most pronounced decrease in tone and therefore highest gastric volumes (3, 17). Assuming that different levels of gastric tone were present, the physical interrelation for volume and pressure implies that the similar stomach volume response in relation to the ingested meal volume reflects a macronutrient dependent difference in intragastric pressure. Since no direct information on gastric tone or intragastric (air) pressure was recorded in this study (owing to its noninvasive approach), this hypothesis remains speculative and points out that concurrent minimal invasive intraluminal pressure measurements are inevitable for future studies. A direct comparison of the presented results with data from barostat studies may not be appropriate since the barostat technique interferes with normal gastric physiology (13). Also, no comparable studies using isovolumic meals of similar caloric but different macronutrient content have been performed using the barostat technique. Nevertheless, we can conclude that macronutrient induced differences in gastric tone are not reflected as a distinct and specific volume response of the stomach under physiological noninvasive conditions.

For the fat meal, although emptying patterns over the first 40 min were similar to those for glucose and protein, higher rates of gastric emptying occurred subsequently. Recent studies using MRI indicated that in the intragastric environment separation of fat content occurs for a variety of meals and can modify the spatial lipid distribution by flocculation causing layering that can distinctly alter the speed of gastric emptying (25, 28). Intragastric creaming of an in vitro validated, acid-stable fat emulsion, like the lipid solution used in this study, was also reported in a recently published study on the behavior of oil in water emulsions in the human gastric lumen (28). This highlights that emulsion stability may be affected not only by low acidity but also by factors such as gastric lipolysis, which are responsible for 25% of acyl chain hydrolysis during meal ingestion (5, 9). In an unpublished in vitro study, we could confirm a breakdown of the lipid 6.82% emulsion beginning 50 min after mixing five 100-ml samples of this emulsion at 37°C with 50 ml fresh gastric juice obtained by aspiration from five healthy volunteers and a further separation with fat layering after 120 min. This time dependency of emulsion separation is likely to be the explanation for the similar gastric volume response observed during the early phase and the accelerated emptying during the late phase of the fat meal.

A number of factors have been addressed as regulators of postprandial satiety such as activation of mechanoreceptors in the gastric body and fundus, the presence of intraintestinal nutrients inducing the release of intestinal hormones and modulation of neuronal pathways (10, 14, 15). In this study we could demonstrate that the perception of satiety and fullness was linearly related to meal and stomach volumes for all the macronutrients. Gastric volume-dependent activation of tension sensitive mechanoreceptors (15, 27, 36) together with rapidly released anorexic peptides as satiety signals (10, 26, 41) might be possible explanations. However, we cannot provide data on gastric tension distribution and its relationship to gastric volumes as well as data on release kinetics of gastrointestinal hormones to clarify our observations. Our data show again that novel noninvasive gastric imaging methods combining acquisition of gastric geometry, intragastric pressure, and assessment of gastrointestinal hormones are needed to understand the mechanisms behind symptom generation. This may also assist to explain inconsistent data on barostat-measured gastric accommodation volumes and on nutrient drink volumes as a surrogate parameter for assessment of postprandial gastric volumes (4, 37).

There were no significant differences in the symptom scores for fullness and satiety between the meals, which are compatible with the observed small differences in stomach volume. Perception scores for nausea reached only moderate levels, with fat provoking the highest response. The volume vs. fullness or satiety curve shifted to the left for the fat meal, whereas there was only a weak association between the sense of nausea and meal or stomach volume. All of these responses are possibly related to postgastric modulation of gastrointestinal sensations (17). Overall the data on gastrointestinal perception suggest that isovolumic, isocaloric liquid meals with different nutrient composition affect gastrointestinal symptoms, at least in part, through postprandial gastric volume and nutrient-specific postgastric modulation.

In summary, in this study gastric volume responses of three specific liquid macronutrient compositions were evaluated for the first time, and, although the results may not be generalized for other nutrient compositions, we showed that these isovolumic macronutrient meals with similar caloric content modulate gastric volume responses by different initial, early, and late meal emptying patterns. The corresponding gastrointestinal symptoms can be related to, but not entirely explained by, the magnitude of postprandial gastric volumes. Even with these distinct differences, the early postprandial characteristics of the volume curves for stomach and meal were uniform for all macronutrients and positions. Therefore under noninvasive physiological conditions macronutrient specific accommodation responses, as shown in gastric barostat studies, are not reflected as gastric volume responses.
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GRANTS

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