Effect of meal volume and calorie load on postprandial gastric function and emptying: studies under physiological conditions by combined fiber-optic pressure measurement and MRI

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Kwiatek MA, Menne D, Steingoetter A, Goetze O, Forras-Kaufman Z, Kaufman E, Fruehaufl, Boesiger P, Fried M, Schwizer W, Fox MR. Effect of meal volume and calorie load on postprandial gastric function and emptying: studies under physiological conditions by combined fiber-optic pressure measurement and MRI. Am J Physiol Gastrointest Liver Physiol 297: G894–G901, 2009; doi:10.1152/ajpgi.00117.2009.—This study assessed the effects of meal volume (MV) and calorie load (CL) on gastric function. MRI and a minimally invasive fiber-optic recording system (FORS) provided simultaneous measurement of gastric volume and pressure changes during gastric filling and emptying of a liquid nutrient meal in physiological conditions. The gastric response to 12 iso-osmolar MV-CL combinations of a multinutrient drink (MV: 200, 400, 600, 800 ml; CL: 200, 300, 400 kcal) was tested in 16 healthy subjects according to a factorial design. Total gastric volume (TGV) and gastric content volume (GCV = MV + secretion) were measured by MRI during nasogastric meal infusion and gastric emptying over 60 min. Intragastric pressure was assessed at 1 Hz by FORS. The dynamic change in postprandial gastric volumes was described by a validated three-component linear exponential model. The stomach expanded with MV, but the ratio of GCV:MV at t0 diminished with increasing MV (P < 0.01). Postprandial changes in TGV followed those of GCV. Intragastric pressure increased with MV, and this effect was augmented further by CL (P = 0.02); however, the absolute pressure rise was <4 mmHg. A further postprandial increase of gastric volumes was observed early on before any subsequent volume decrease. This “early” increase in GCV was greater for smaller than larger MV (P < 0.01), indicating faster initial gastric emptying of larger MV. In contrast, volume change during filling and in the early postprandial period were unaffected by CL. In the later postprandial period, gastric emptying rate continued to be more rapid with high MVs (P < 0.001); however, at any given volume, gastric emptying was slowed by higher CL (P < 0.001). GCV half-emptying time decreased with CL at 18 ± 6 min for each additional 100-kcal load (P < 0.001). These findings indicate that gastric wall stress (passive strain and active tone) provides the driving force for gastric emptying, but distal resistance to gastric outflow regulates further passage of nutrients. The distinct early phase of gastric emptying with relatively rapid, uncontrolled passage of nutrients into the small bowel, modulated by meal volume but not nutrient composition, ensures that the delivery of nutrients in the later postprandial period is related to the overall calorie load of the meal.

gastric accommodation; gastric emptying; intragastric pressure

The stomach responds to a meal by tonic relaxation (accommodation) to allow expansion of the gastric reservoir volume without a significant increase in wall stress and intraluminal pressure (2, 3). MRI studies under physiological conditions and after pharmacological modulation of gastric activity have shown that the magnitude of this postprandial relaxation is closely associated with the gastric emptying rate of water and liquid nutrients (20, 22). In contrast, the frequency and vigor of antral contractility did not affect this process (20, 22, 23, 34). These findings suggest that gastric emptying is driven by tonic contraction of the gastric fundus, the so-called “pressure-pump” hypothesis of gastric emptying (20).

Formal assessments of gastric tone and the mechanism of gastric emptying require simultaneous assessment of total gastric volume (TGV) (i.e., the stomach wall), gastric content volume (GCV) (i.e., the meal and secretion), and intragastric pressure in the postprandial period. An important limitation of previous studies is that conventional measurement techniques assess these parameters separately. Gastric MRI combined with manometry can assess these parameters over time (20); however, mathematical models indicate that the gastric pressure required to drive gastric emptying is very low (<2 mmHg) (30). Conventional manometry has inadequate pressure resolution and is confounded by background noise and respiratory artefacts (2, 3). Barostat measurement of gastric tonic activity is invasive and involves the positioning of a large volume bag in the proximal stomach that is expanded and maintained at a constant pressure. This process itself drives gastric relaxation, exaggerates changes of gastric geometry and tone after a meal (i.e., accommodation), and affects the dynamics of gastric emptying, especially in the early postprandial period (28).

Recently, a microfiber-optic recording system (FORS) for high-sensitivity medical pressure measurements has become available (39). This study combined MRI and FORS to assess the dynamic gastric volume and pressure response (i.e., analogous to gastric barostat) to a liquid nutrient meal in healthy volunteers. FORS was placed in an open pressure chamber adjacent to a small (20 ml) balloon on a customized catheter that could be visualized and positioned by MRI. This assembly ensures accurate measurement of intragastric cavity pressure by maintaining position at the air-fluid interface and preventing impaction against the gastric wall. The effect of a wide range of volumes and calorie load of iso-osmolar liquid nutrient meals during gastric filling and emptying was assessed in healthy volunteers. The pressure-pump hypothesis predicts that I) increasing gastric filling with isocaloric liquid is associated with a small but significant rise in intragastric pressure and

THE STOMACH RESPONDES TO A MEAL BY TONIC RELAXATION (ACCOMMODATION) TO ALLOW EXPANSION OF THE GastrIC RESERVOIR VOLUME
more rapid gastric emptying and 2) increasing calorie load is associated with a lower rise in intragastric pressure per unit of volume (i.e., greater tonic relaxation) and less rapid gastric emptying. Concurrently, minimally invasive pressure and volume measurements of gastric function provided direct evidence to test these predictions under physiological conditions.

MATERIALS AND METHODS

Subjects and Protocol

Sixteen healthy subjects (9 M and 7 F; age: 20–37 yr, BMI: 18–24 kg/m²) participated in this study. All subjects gave written informed consent. The study protocol was approved by the local Ethics Committee at the University Hospital Zürich, Zürich, Switzerland. A prospective, single-blind, randomized study with balanced factorial design was performed. Fasted subjects participated in three studies on test days separated by at least a week. On each day, a nasogastric assembly (described below) containing channels for intragastric pressure measurement and infusion was placed transnasally with its tip positioned in the gastric corpus. Subjects were placed in the MRI scanner bed in the right decubitus position for baseline measurements of intragastric pressure, stomach volume (TGV), and volume of liquid gastric contents [GCV (meal plus secretion)]. One of twelve liquid nutrient test meals (see below) was then administered via the nasogastric assembly at ~100 ml/min. The meals were delivered in randomized sequence according to a balanced factorial design that preserved the power of a classical crossover study without multiplying visits for each volunteer (Tables 1 and 2). TGV and GCV were assessed by MRI during gastric filling after infusion of each 100 ml. Thus the 200-ml meal was infused over ~6 min and the 800-ml meal over ~24 min. The actual difference between 200- and 800-ml meals in the time taken to complete infusion was less than predicted (median: actual infusion time of 10 min vs. predicted infusion time of 16 min). This discrepancy between actual and predicted duration of infusion is due to the greater viscosity of the small meals attributable to higher caloric density; therefore, small meals were effectively delivered at a slower rate than predicted. Gastric volumes were then measured over the postprandial period every 1 min up to 60 min. Intragastric pressure was measured concurrently and continuously throughout. Electronic markers synchronized the volume and pressure measurements.

Meal Composition

The gastric response to 12 volume (200, 400, 600, 800 ml) and calorie load (200, 300, 400 kcal) combinations of multinutrient drink was assessed [Ensure TwoCal, 41.5% carbohydrate, 41.2% fat, 17.3% protein, calorie density 2 kcal/ml; Abbott, Baar, Switzerland diluted as required with iso-osmolar 1.61% saline (Kantons Apotheke, University Hospital Zürich, Zürich, Switzerland)]. The meals were labeled with paramagnetic contrast (0.5 mmol/l Gd-DOTA; Dotarem; Laboratorie Guerbet, Aulnay-sous-Bois, France).

MRI

Studies were performed using a 1.5T whole MRI system (Intera; Philips, Best, The Netherlands). Six rectangular surface coils (height = 20 cm, width = 10 cm) fixed around the abdomen and connected to independently receive channels were used for signal detection. TGV and GCV were assessed with volume scans using a multistack and multislice balanced steady-state free precession imaging technique. A total of 40 sagittal and 15 transverse image slices were acquired in 3 s with slice thickness = 5 mm and in-plane resolution = 1.56 × 1.9 mm² (matrix size, 256 × 205 pixel; echo time/repetition time, 1.9/4.0 ms; flip angle, 35°). Volunteers were asked to continue breathing at their regular rhythm during each volume measurement to minimize motion artifacts on the images and pressure artifacts during intragastric pressure measurements.

FORS

FORS comprised a sensor chip of 0.42 mm OD micromachined in silicon and attached to an optical fiber 0.25 mm OD (Fig. 1A; Samba Sensors, Göteborg, Sweden). This novel pressure sensor uses the interferometric Fabry-Perot principle, which states that the deflection of a microcavity membrane by pressure results in a change in the reflected light intensity when the interference conditions inside the cavity are modified (39). The specifications of the sensor were as follows: measurement range −36.8–257.6 mmHg, accuracy 0.38 mmHg + 2%, temperature drift 0.15 mmHg/°C in the range 20–45°C, and long-term stability 0.5% at 24 h (www.samba.se). Pressure measurements were continuously streamed at 1 Hz to a controller unit and dedicated laptop, which remained outside of the scanner room.

The pressure sensor was inserted into one of four lumina in a custom-made Dentysleeve catheter (Fig. 1B; 5 mm OD; Mui Scientific, Mississauga, ON, Canada). The lumen was sealed to atmospheric pressure, but closely spaced sideholes allowed equilibration of pressure within the lumen. Additional lumina allowed intragastric infusion of the test meals and inflation of the balloon (maximal volume 30 ml). The positioning of the pressure sensor immediately proximal to the balloon maintained its position at the air-liquid interface in the stomach and prevented direct contact with the gastric wall. The balloon was visible on MRI scanning, and position could be adjusted if required.

### Table 1. Randomization of tested caloric density-volume meal combinations using a balanced fractional design

<table>
<thead>
<tr>
<th>Visits</th>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>v8c2</td>
<td>v4c3</td>
<td>v6c4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>v8c4</td>
<td>v2c3</td>
<td>v4c2</td>
<td></td>
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<tr>
<td>3</td>
<td>v6c4</td>
<td>v2c2</td>
<td>v4c3</td>
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<tr>
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<td>v4c2</td>
<td>v6c4</td>
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<td>v4c4</td>
<td>v6c3</td>
<td>v2c2</td>
<td></td>
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<tr>
<td>8</td>
<td>v2c4</td>
<td>v8c3</td>
<td>v6c4</td>
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<td>9</td>
<td>v6c3</td>
<td>v4c2</td>
<td>v8c4</td>
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<td>v4c4</td>
<td>v6c3</td>
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<td>11</td>
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<tr>
<td>16</td>
<td>v4c4</td>
<td>v8c3</td>
<td>v6c3</td>
<td></td>
</tr>
</tbody>
</table>

Each of 16 subjects was tested 3 times for three caloric density-volume combinations. All 12 possible permutations of concentrations were used. The 4 volumes are repeated 4 times in each column, whereas the 3 concentrations are column-wise optimized for a balanced design for 4 volumes (v2, v4, v6, v8, where v2 stands for 200 ml etc.), three concentrations (c2, c3, c4, where c2 stands for 200 kcal etc.) are optimized column-wise for an incomplete (because not all subjects received the same meal combination) but balanced design.

### Table 2. Number of records by filling volume (rows) and caloric content included in the final analysis

<table>
<thead>
<tr>
<th>Filling Volume (ml)</th>
<th>200 kcal</th>
<th>300 kcal</th>
<th>400 kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ml</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>400 ml</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>600 ml</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>800 ml</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Intragastric pressure measurement. A: fiber-optic pressure recording system (FORS) (left) comprised a small (0.42 mm OD) silicon-bonded pressure sensor attached to a fiber-optic cable (right). This catheter was placed into a custom-made assembly (B). The dedicated lumen exposed the FORS to intragastric pressure through a chamber with side hole perforations. The adjacent lumina allowed injection of air into a 20-ml balloon pressure measurement location, mounted distally, and intragastric infusion of the test meals.

**Data Analysis**

**Volume scan.** TGV was evaluated semiautomatically by outlining the inner contour of the gastric wall within each slice, multiplying the segmented area by the slice thickness, and adding all “slice volumes” to calculate TGV. Because intragastric air (black) and labeled liquid meal (bright signal) had a distinct contrast, a manually selected intensity threshold was used to identify and compute GCV (22, 23, 36). Volume analysis was performed using in-house software implemented in IDL 5.5 (Research Systems, Boulder, CO) (36). This analysis method has excellent interobserver reproducibility of 12% at small volumes (<200 ml), reducing to 6% at larger volumes (>600 ml) across varied gastric volumes (13, 14).

**Intragastric pressure.** During gastric filling, the median pressure was assessed in a 30-s window 2 min after each 100 ml was infused utilizing the pause in infusion required for MRI volume scans. Measurements were referenced to intragastric baseline on the basis of the individual pressure recordings before the meal infusion. During the postprandial period, intragastric pressure was assessed as a continuum from the initial pressure immediately after completed filling. Variation in pressure attributable to breathing and also artifacts related to coughing and shifts in catheter position could be clearly identified in the data; these were removed by applying a local median filter to the raw data.

**Statistical Analysis**

A nonlinear mixed-effects model was fitted to all the data in the study (i.e., “population” fit) using function nlme in the program “R” (R, lib. Nlme, Version 2.0.1, 2004), with “subject” and “treatment within subject” marked as random parameters. A diagonal covariance structure was assumed for random effects (31). This method correctly handles serial correlation within each curve showing temporal changes in gastric volumes and is similar to the approach used in population pharmacology (4, 7). This approach is superior to fitting individual gastric volume curves because these have a large coefficient correlation, giving ambiguous parameter estimates attributable to correlation. This method reduces parameter variance, a phenomenon called “shrinkage” (10).

The parameter coefficients were derived from mixed-effects model with standard errors for differences between volumes computed from linear contrasts using the program “R” (R, lib. lme, Version 2.0.1, 2004). Matching of data from the gastric model to the raw data was assessed by assessment of residual errors (28). A P value ≤0.05 was considered statistically significant.

**Volume scan.** Postprandial (t < 60) TGV and GCV were plotted against time. Key parameters during filling and emptying were defined on the basis of a least-square fit of each volume curve to the following gastric emptying model (R, lib. nlme, Version 2.0.1, 2004) (31a, 31):

\[ V(t) = V_0 (1 + kT_{empt}e^{-t/T_{empt}}) \]

In this expression, \( V_0 \) is the initial postprandial volume at time \( t_0 \) (ml). The independent parameters \( k \) and \( T_{empt} \) describe volume change over the entire postprandial period. The \( T_{empt} \) parameter is a time constant that quantifies overall rate of emptying (min) similar to standard models used for the analysis used to describe gastric emptying. The addition of the \( k \) parameter is required to quantify any initial increase in volume from \( V_0 \) (15, 16, 23). The study period was subdivided into the filling and emptying (t < 60) phases. The early and late emptying periods are defined by the characteristic pattern of volume change after a meal, with the late period beginning at the point at which a steady rate of fall in GCV is established. The half-emptying time (T50) was determined from parameters \( k \) and \( T_{empt} \) by setting \( V(t)/V_0 \) in the equation above to 0.5 and applying the Newton-Rhapson iteration method to find \( t = T_{50} \). The maximum gastric emptying rate (GEr,max), given as percentage decrease in GCV per minute, denotes the maximum slope of the gastric emptying curve.

In a separate analysis, the effect of study interventions on parameters describing gastric volume change were assessed using the linear mixed-effect model with subject as a random variable, and meal volume and calorie load with either 1) GCV, 2) TGV, or 3) time as fixed variables. Interaction terms were tested but did not improve the quality of the fit as measured with the Akaike Information Criterion (1).

The results in Tables 3 to 5 are group mean averages estimated by the linear mixed-effect model and differ slightly from the raw data presented in the figures. In addition, the calorie density was computed from the calorie content and filling volume, with nine levels as 0.25, 0.33, 0.38, 0.5, 0.67, 0.75, 1, 1.5, and 2 kcal/ml. Calorie load (the primary fixed variable tested) was a better predictor of gastric volumes and emptying than calorie density in the mixed-effect model, and therefore results for calorie density are not presented in detail.
EFFECTS OF MEAL VOLUME AND CALORIE LOAD ON GASTRIC FUNCTION

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Table 3. Effects of meal volume on initial postprandial gastric volume response and intragastric pressure

<table>
<thead>
<tr>
<th>Meal Volume</th>
<th>GCV V₀</th>
<th>TGV V₀</th>
<th>P₀</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 ml</td>
<td>250 (23)</td>
<td>438 (20)</td>
<td>-0.07 (1.06)</td>
<td>1.38 (0.09)</td>
</tr>
<tr>
<td>400 ml</td>
<td>380 (25)*</td>
<td>568 (20)*</td>
<td>1.34 (1.04)</td>
<td>1.06 (0.11)*</td>
</tr>
<tr>
<td>600 ml</td>
<td>555 (30)*</td>
<td>743 (20)*</td>
<td>1.63 (1.04)</td>
<td>0.86 (0.11)*</td>
</tr>
<tr>
<td>800 ml</td>
<td>664 (34)*</td>
<td>852 (20)*</td>
<td>2.77 (1.04)*</td>
<td>0.91 (0.11)*</td>
</tr>
</tbody>
</table>

Data and standard error between any 2 volumes (in parenthesis) are estimated from mixed-effects model. The influence of caloric load was not significant on gastric volume change during the early postprandial period (data not shown). GCV, gastric contents volume (meal plus secretion volume); TGV, total gastric volume (GCV plus air); V₀, gastric volume immediately after completed meal infusion; P₀, intragastric pressure immediately after completed meal infusion. *P ≤ 0.05 vs. 200 ml; †P < 0.01 vs. GCV; ‡P < 0.001 vs. 0 mmHg.

Intragastric pressure. The effects of filling volume and calorie load on intragastric pressure during the filling phase were assessed using the linear mixed-effect model with subject as a random variable with filling volume and calorie load as fixed variables. The rate of change in postprandial intragastric pressure was quantified by the slope of a linear fit with the initial intragastric pressure (P₀) at V₀ estimated by extrapolation to t₀. The slope of the postprandial intragastric pressure was correlated to parameters defining volumetric response.

RESULTS

Subjects tolerated the nasogastric intubation and intragastric infusions of the test meals. Image acquisition and analysis were performed successfully in all subjects.

Filling Phase

Residual GCV was small, and there was no difference on each study day in the baseline gastric volumes (data not shown). Independent of calorie load, larger meal volumes produced larger initial gastric volumes [GCV at t₀ (GCV₀); P < 0.0001, Table 3]; however, the ratio between the final volume of the infused meal (200, 400, 600, 800 ml) and resultant GCV₀ decreased progressively (125, 95, 92, 83%, respectively). TGV was consistently greater than GCV by an average of 188 ± 20 ml (P < 0.0001). This difference, which is the volume of air in the stomach, was remarkably stable from baseline through gastric filling and emptying for each individual study.

Baseline intragastric pressure was 5.2 ± 0.4 mmHg. Intragastric pressure (P₀) increased with meal volume; however, a significant increase from 0 mmHg was observed only for the 800-ml meals (P = 0.01, Table 3). Intragastric pressure on filling was modulated by calorie load, which increased the intragastric pressure at a rate of 0.14 mmHg/100 ml for every 100-kcal increase (P = 0.02, Fig. 2). The maximum rise in intragastric pressure remained <4 mmHg even for high-volume, high-calorie meals. A post hoc review confirmed that the balloon and pressure sensor were positioned at the gastric air-fluid interface over the duration of the study.

Gastric Emptying

After delivery of the test meal, gastric emptying commenced immediately as evidenced by the appearance of Gd-DOTA marked fluid in the small bowel. Despite important interindividual variation (Fig. 3), the dynamics of gastric volume change followed a consistent pattern in the postprandial period. After the infusion, a further increase in gastric volumes (TGV and GCV) was often observed in the early postprandial period. This was followed by a progressive volume decrease in the late postprandial period (Fig. 4). The early rise in gastric volumes from V₀ (described by the k-coefficient) was greater for smaller than larger meal volumes (P < 0.01, Table 3). The magnitude of this event was similar for TGV and GCV and independent of calorie load.

Gastric emptying half time (GCV T₅₀) tended to decrease with increasing meal volume (P = 0.09, Table 4), and a significant difference was present between 200 and 800 ml (P = 0.03). Calorie load increased GCV T₅₀ by 18 ± 6 min for each additional 100-kcal load (P < 0.0001, Table 4). Similar to direct measurements, TGV T₅₀ varied with GCV T₅₀; however, TGV T₅₀ was longer by an average of 32 ± 6 min across all meal volume and composition combinations.

In the later postprandial period, once GCV was falling at a steady rate, both meal volume and calorie load affected the rate of gastric emptying (GEₚ₋₅₀). Rising meal volume produced a significant increase in GEₚ₋₅₀ (P < 0.001). Rising calorie load was associated with a significant decline in GEₚ₋₅₀ (P < 0.001). Data presented in Tables 4 and 5 show the effects of meal volume and calorie load on gastric emptying in terms of T₅₀ and GEₚ₋₅₀ respectively. Although both show significant effects, a consistent dose-response effect for variation in calorie loading is evident only for the latter. This demonstrates an important interaction between meal volume and calorie load (P < 0.001), such that, the decrease in GEₚ₋₅₀ with calorie load is less marked at large than small volume meals.

Postprandial intragastric pressure was independent of filling volume (P = 0.4) and its calorie load (P = 0.6), allowing pooling of all data. The intragastric pressure decreased very slowly at an average rate of 1.1 ± 0.4 mmHg/60 min (P <

Fig. 2. Intragastric pressure changes during the filling phase. The minimal rise in intragastric pressure with greater volume infusions was augmented by an additional increase in the calorie load of the test meal. The pressure increase was progressive; however, the magnitude was small (average increase <3 mmHg with a high-calorie, 800-ml meal).
0.01) during gastric emptying (Fig. 5). The rate of decrease was not associated with the volumetric response.

**DISCUSSION**

Continuous, high-resolution measurements of volume and pressure during gastric filling and emptying were acquired with a combination of MRI and minimally invasive FORS (Fig. 1). These direct measurements under physiological conditions reveal the effects of meal volume and calorie load on gastric function and emptying in the early and late postprandial periods. In light of these results, we propose an important revision of the pressure-pump hypotheses of gastric emptying.

**Gastric Filling**

MRI measurements demonstrated that expansion of TGV with GCV during infusion of the test meal was independent of calorie load. Concurrent FORS pressure measurement revealed a small but significant rise in intragastric cavity pressure during gastric filling (Table 3). For the low-calorie meals (200 kcal), there was little change in pressure across the range of volumes studied (200–800 ml); however, as calorie load increased, the intragastric pressure progressively rose with ingested volume (Fig. 2). The finding that intragastric pressure increases to a greater degree on filling with a high-calorie than a low-calorie nutrient meal indicates that this effect is related not to the mechanical distension by gastric filling, per se, but to changes in gastrointestinal function triggered by nutrient feedback. As discussed below, these effects are likely mediated by stress in the gastric muscle wall (including passive strain and active tone) and distal resistance to flow from the pyloric and duodenal activity.

Measurements of postprandial symptoms were not formally assessed; however, previous work (11, 16) and preliminary studies using the combined MRI/FORS method (12) report that fullness and satiation are related to the volume infused, whereas dyspeptic symptoms including nausea and bloating occur almost exclusively with high-volume-load, high-calorie-load (especially high-lipid) meals or duodenal infusion. These reports suggest that normal postprandial fullness is related to distension or strain of the gastric wall at near constant pressure, whereas dyspeptic symptoms are related to a build up of tension in the gastric wall with increased intragastric pressure (21). The differential role of mechanical and chemical stimulation on gastric function and symptoms is the subject of ongoing research.

**Early Postprandial Period**

As expected, the volume of gastric contents at $t = 0$ ($GCV_0$) increased with the volume of the test meal; however, the relationship of $GCV_0$ expressed as a proportion of the infused...
meal volume was not constant (Table 3). Independent of the calorie load, GCV0 was greater than a 200-ml meal volume (125%) but significantly smaller than an 800-ml meal volume (83%). Thus, as meal volume rises, a progressively larger proportion of liquid nutrient was seen to pass into the small bowel during a relatively rapid, early phase of emptying. After gastric filling, a further increase in GCV was often seen in the early postprandial period (quantified by the \( t \) coefficient in Table 3) before gastric volumes started to decline (Fig. 4). Similar to observations at \( t = 0 \), this increase was independent of calorie load and significantly greater for the smaller than the large volume meals. GCV can be expressed as a dynamic balance between the volume of the meal, the volume of gastric secretion, and the volume of gastric emptying. Recent MRI studies have demonstrated that GCV rises after meal ingestion if the rate of secretion exceeds the rate of gastric emptying and that the \( t \) coefficient in the emptying model provides a useful assessment of secretion volume (15). Thus the rate of gastric emptying was slower than the rate of gastric secretion at smaller filling volumes, whereas the reverse was true at larger filling volumes.

It should be noted that small-volume meals were delivered into the stomach over a shorter time than the large-volume meals. This will have reduced volume measurements during the early postprandial period more for the large than the small meals. However, the time required for infusion was small compared with overall study duration, and, moreover, longer infusion times would allow more time for gastric secretion to collect. These two factors work in opposite directions and, to some extent, counteract each other.

This study suggests that the early phase of gastric emptying plays a key role in determining the subsequent gastrointestinal response to a meal (8, 28). The passage of nutrient into the small bowel triggers neurohormonal responses, mediated by the vagus, the myenteric plexus, and the release of small bowel peptide hormones (e.g., CCK, glucagon-like peptide-1), which effect gastrointestinal function and gastric emptying (5). These responses vary with the volume, calorie density, and speed of delivery of the nutrients to the duodenum (19, 24–27). The results presented suggest that the early phase of gastric emptying provides a sample of the liquid nutrient test meal to the small bowel, at a volume and delivery speed that are determined by the meal volume but not its nutrient composition. This would provide an elegant means by which the small bowel feedback response can integrate both the mechanical (volume) and the chemical (calories) properties of the meal such that subsequent nutrient delivery is related to the overall calorie load. This finding is consistent with observations from the nutritional sciences where satiation was shown to be related to the meal volume (or weight) and calorie density together (i.e., calorie load) rather than either of these variables alone (9).

There is an apparent discrepancy between the lack of effect of calorie load on volume measurements and its effects on intragastric pressure during the early postprandial period. For individual studies, pressure and volume measurements were consistent over time, and thus measurement error is unlikely. It should be emphasized that, for any given calorie load, 1) intragastric pressure increased with meal volume and 2) gastric emptying was faster for

Table 4. Effects of meal volume and calorie load on the half-emptying time of the gastric contents

<table>
<thead>
<tr>
<th>GCV ( T_{50} ) (min) Calorie load</th>
<th>Meal Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 ml</td>
</tr>
<tr>
<td>200 kcal</td>
<td>56 (7)</td>
</tr>
<tr>
<td>300 kcal</td>
<td>74 (7)†</td>
</tr>
<tr>
<td>400 kcal</td>
<td>92 (7)†</td>
</tr>
</tbody>
</table>

Gastric emptying was profoundly delayed by an increasing calorie load. Data and standard error between any 2 volumes (in parenthesis) are estimated from mixed-effects model. The standard errors for differences between 2 volumes are given in parenthesis. \( T_{50} \), half-emptying time. *\( P \leq 0.05 \) vs. 200 ml; †\( P < 0.01 \) vs. 200 kcal.
larger meal volumes. Thus there is an interaction between meal volume and calorie load, and the effects of these variables on gastric function should not be considered in isolation. In principle, the increase in intragastric pressure with high-calorie meals could be attributable to decreased gastric relaxation (accommodation) or increased distal resistance to gastric emptying. A large number of barostat and manometry studies suggests that the latter is more likely (18, 32, 38). The discrepancy in timing of pressure and volume changes in this study under physiological conditions likely reflects the dynamic interaction of gastric and duodenal response to the meal. Confirmation requires high-sensitivity measurements of the gastroduodenal pressure gradient with multiple sensors.

Late Postprandial Period

Observations in the late postprandial period were consistent with previous studies in that gastric emptying proceeded at a constant rate that is typical for nutrient liquids (33, 35). At the same time, there was gradual fall in intragastric pressure back to baseline (Fig. 5). These effects were finely graduated across a wide range of meal volumes and calorie loads, indicating that the stomach adapts to the physical and chemical properties of the ingested meal to maintain a constant rate of nutrient delivery to the small bowel.

High meal volumes promoted gastric emptying; however, the nutrient feedback “brake” had important effects on gastric emptying also in the late postprandial period. These effects are evident when presented in terms of both \( T_{50} \) and \( \text{GER}_{\text{max}} \) (Tables 4 and 5); however, a dose-response relationship between calorie load and gastric emptying was evident only for \( \text{GER}_{\text{max}} \). These findings demonstrate that increasing meal volume results in an important increase in nutrient delivery per unit time. Thus, at low meal volumes, doubling the calorie load (density) approximately halves the rate of gastric emptying (maintaining calorie delivery at a steady rate); whereas, at higher meal volumes, doubling the calorie load (density) reduced gastric emptying by only a quarter (resulting in rapid nutrient delivery). This finding is consistent with predictions from mathematical models of liquid nutrient gastric emptying (29) and classic research that assessed gastric emptying by sampling duodenal contents (19). The disproportionate increase of calorie delivery with meal volume has important implications. First, it indicates that maximizing meal volume will optimize nutrient delivery in endurance exercise and other conditions (e.g., catabolic disease) in which this is desirable (29). Second, it suggests that regular intake of large portion sizes may overwhelm physiological controls of calorie intake and satiation increasing the risk of obesity as observed in dietary intervention studies (9).

Measurement of Gastric Function and Emptying

MRI measurement of gastric volume changes after a meal provides important information that informs the interpretation also of conventional clinical measurements. For example, it shows that it is not appropriate to normalize GCV at \( t_0 \) because this approach will systematically overestimate gastric emptying times expressed as \( T_{50} \) for small meals relative to larger meals. Furthermore, the results indicate that \( T_{50} \) is a complex, composite end-point that is affected not only by the rate of gastric emptying, but also by the volume of gastric secretion, which varies between individuals and for different test meals. These findings explain, in part, the high variation in gastric emptying time reported by scintigraphy and breath test studies and the difficulty in comparing the gastric response to test meals of different volumes, composition, and secretogogical activity.

Noninvasive measurement reveals that the dynamic volume of change of TGV followed that of GCV throughout the study (similar \( \kappa \) and \( \text{GER}_{\text{max}} \)), and the volume of air in the stomach remained remarkably constant (Fig. 4). These findings indicate that change in intragastric volume drives gastric relaxation (accommodation) after a meal and, conversely, that nutrient feedback on gastric tone does not produce important changes in TGV in the absence of an additional distension force (e.g., barostat). Indeed, any technique that itself imposes major changes in gastric volume will inevitably disrupt the control of gastric emptying in the early postprandial period and subsequent gastric function. Rather the effects of gastric wall stress (passive filling and active tonic relaxation or contraction) can be inferred from the effects on intragastric pressure and gastric emptying rate.

This study investigated liquid nutrient meals. This focus is appropriate in the first instance as solids are broken down into a liquid or fine suspension (usually <2 mm in diameter) before passing through the pylorus (26). Moreover, after the lag phase, solid meals empty at a similar rate to fluids of comparable calorie density and composition (37). Thus the mechanism and control of gastric emptying (as opposed to gastric digestion) are likely to be similar for liquids and solids. Nevertheless, studies are now required for solid meals, particularly as the emptying of solids may be more sensitive for the detection of delayed gastric emptying in the clinical setting (35).

Table 5. Effects of meal volume and calorie load on the maximal gastric emptying rate of the contents within the stomach in the later postprandial period

<table>
<thead>
<tr>
<th>( \text{GER}_{\text{max}} ) (%/min)</th>
<th>Meal Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calorie Load</td>
<td>200 ml</td>
</tr>
<tr>
<td>200 kcal</td>
<td>3.9 (0.4)</td>
</tr>
<tr>
<td>300 kcal</td>
<td>2.9 (0.4)†</td>
</tr>
<tr>
<td>400 kcal</td>
<td>1.9 (0.4)↑</td>
</tr>
</tbody>
</table>

Data and standard error between any 2 volumes (in parenthesis) are estimated from mixed-effects model. The standard error for absolute estimates is 0.4%/min, and for differences is 0.6%/min. \( \text{GER}_{\text{max}} \), maximal emptying rate. *\( P \leq 0.05 \) vs. 200 ml; †\( P < 0.01 \) vs. 200 kcal.

Conclusion

High-resolution measurement of gastric volume and pressure across a physiological range of test meals provided new insight into the mechanism and control of gastric emptying and nutrient delivery into the small bowel.

The increase in intragastric pressure and gastric emptying rate with meal volume for a given calorie load provides direct support for the pressure-pump mechanism of gastric emptying described in the introduction. In contrast, the increase in intragastric pressure during filling with high- but not low-calorie meals for a given meal volume was not expected. Because the volume response to high- and low-calorie meals was identical, the increase in intragastric pressure indicates an increase in active gastric wall tension. These effects did not result in more rapid gastric emptying; on the contrary, gastric emptying was slower for high-calorie meals. Together these findings indicate that gastric wall stress (includes
passive strain and active tone) provides the driving force for gastric emptying, but distal resistance to flow generated by the pylorus and duodenum regulates passage of nutrients into the small bowel. This inference is consistent with the findings of mathematical models of gastric function on the basis of combined antroduodenal manometry and MRI data that estimate antroduodenal pressure gradients in the range of <3 mmHg in healthy subjects (17, 20, 22).

The present study also provides evidence that the rapid, relatively uncontrolled early phase of gastric emptying during and immediately after ingestion of a liquid nutrient test meal provides a sample of gastric contents to the small bowel, the volume of which is determined by the meal volume but not its nutrient composition. This simple mechanism ensures that the gastrointestinal response to the meal is related to its overall caloric load and is likely to explain why satiation is achieved by intake of an appropriate amount of nutritious food and not by a large volume of water or a small serving of Swiss chocolate.

REFERENCES