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Chapter 2

Comparison of total and compartmental gastric emptying and antral motility between healthy men and women

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Abstract

There is increasing evidence of gender-related differences in gastric emptying. The purpose of this study was first, to confirm the difference in gastric emptying for both solid and liquid test meals between healthy men and women, and secondly, to investigate the origin of this difference by studying regional gastric emptying and antral motility.

Methods. A standard gastric-emptying test with additional compartmental (proximal and distal) evaluation and dynamic imaging of the antrum was performed in 20 healthy women studied in the first 10 days of the menstrual cycle, and in 31 healthy age matched men.

Results. In concordance with previous reports, women had a longer half-emptying time for solids as compared to men (86.2 ± 5.1 vs. 52.2 ± 2.9 min, P < 0.05). In our observations this seemed to be related to a significantly prolonged lag phase and a significant decrease in terminal slope. Dynamic antral scintigraphy did not show a significant difference. The distribution of the test meal within the stomach (proximal vs. distal) showed more early proximal retention in women as compared to men. The terminal slope of the distal stomach was significantly lower in women. We did not observe a significant difference in gastric emptying of the liquid test meal between men and women.

Conclusion. Gastric emptying of solids is significantly slower in healthy women as compared to men. These findings emphasize the importance of using different normal values for clinical and research purposes in gastric emptying scintigraphy in men and women. The difference could not be explained by antral motility alone. Increased proximal retention and a lower terminal emptying rate in women are observations to be further investigated.
Normal gastric emptying in male and female

Introduction

Studies of gastric emptying using scintigraphic techniques with radiolabeled standard meals were introduced by Griffith in 1966\(^1\) and refined by Meyer\(^2\) and Harding\(^3\) with the introduction of simultaneous measurement of gastric emptying of both solids and liquids in 1976. Dual isotope scintigraphy is now widely used for clinical and investigative purposes. It is a noninvasive, physiologic, easy to perform, safe and quantitative technique with a low radiation burden.\(^4\), \(^5\) It has become the gold standard for the evaluation of gastric emptying for solids and liquids in all types of gastrointestinal disorders and for assessing the efficacy of gastrokinetic drugs and surgical procedures.\(^5\), \(^6\) Further investigation of the pathophysiology of functional dyspepsia focused on antral dysmotility, abnormal gastric pacemaker function and myoelectric activity.\(^7\)–\(^10\) These investigations have led to the conclusion that delayed gastric emptying of a solid meal is related to antral hypomotility.\(^11\), \(^12\) It was demonstrated that dynamic gastric scintigraphy allows visualization and characterization of antral contractions.\(^13\), \(^14\) It can also be used simultaneously to evaluate the compartmentalization of food inside the stomach and to quantify the emptying of a radiolabeled test meal from each compartment.\(^15\)

The normal values for scintigraphic gastric emptying studies are based on male controls or a mixed control population. Historically it has been assumed that men and women have identical rates of gastric emptying.\(^2\), \(^3\), \(^16\)–\(^19\) The effect of gender on gastric emptying remains controversial though there is more and more evidence that women have slower gastric emptying rates for solids\(^20\), \(^22\) and possibly also for liquids.\(^23\)

The aims of this study were (1) to confirm the difference in gastric emptying for solid and liquid test meal between healthy men and women and (2) to investigate the origin of this difference in absence of pathology by studying regional gastric emptying and antral motility.
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Materials and Methods

Subjects

We studied 20 healthy female volunteers (mean age 22.8 ± 0.38 yr) and compared the scintigraphic results with 31 healthy male volunteers (mean age 22.6 ± 0.93 yr). Every volunteer was questioned about medical history, use of drugs and gastrointestinal symptomatology. Exclusion criteria were a history of chronic or recent gastrointestinal disease or complaints, abdominal surgery and use of drugs with known interference on gastrointestinal motility. Female volunteers were studied in the first 10 days of the menstrual cycle to exclude pregnancy and minimize progesterone effect. All volunteers gave written informed consent to participate in the study, which was approved by the medical ethics committee of the Leuven University Hospital.

Scintigraphic test procedure

All volunteers were studied after an overnight fast of at least 8 h. Gastric emptying was evaluated after ingestion of a standardized test meal consisting of 50 g scrambled egg labeled with 74 MBq $^{99m}$Tc-sulfur colloid (Mallinckrodt), 2 slices of regular white bread and 150 mL water labeled with 3.5 MBq $^{111}$In-DTPA (Mallinckrodt). The meal contains approximately 230 kcal with 35% fat, 47% carbohydrate and 18% protein. Simultaneous 1-min anterior and posterior static images (128x128 pixels) of the stomach were acquired on the 140-keV $^{99m}$Tc and 245-keV $^{111}$In peaks with the subjects sitting between the two detectors of a dual-head gamma camera. Images were taken every 10 min for 1 h and every 15 min for the second hour. Anterior dynamic (64x64 pixels) frames of 1 sec each were also acquired for 4 min after every static acquisition.

Data analysis

Static images. Regions of interest (ROIs) were drawn around the total stomach for both isotopes, and also around the proximal and distal stomach for technetium at each time interval on anterior and posterior images. After correction for technetium decay and indium down scatter, geometric mean counts were determined for each region and percentages of meal retention were calculated at each time interval. Total stomach data
for solids were analyzed using the power exponential function \( y(t) = 1 - (1 - e^{kt})^\beta \), which permits determination of the solid lag-phase (Tlag), emptying rate (ER) and half-emptying time (T/2).\(^{15}\) The parameters \( k \) and \( \beta \) of this function were determined by a nonlinear least-squares fitting algorithm. Total stomach liquid emptying data were fit to a single exponential function to determine the emptying rate and half-emptying time. Compartmental stomach data for solids were analyzed on time-activity curves. The terminal slope of the distal stomach emptying was determined by linear regression of the mean time activity curve after peak activity for male and female volunteers.

**Dynamic images.** The methodology used to process dynamic images has been described by our institution elsewhere.\(^{14}\) In summary, to allow for precise outlining of the antrum, each set of dynamic images was first reframed in a single 4-minute image and a ROI was drawn around the horizontal portion of the stomach between the incisura angularis and the pylorus. This region was then divided into three subregions representing the proximal, mid and distal antrum. A time-activity curve was generated for all subregions for each dynamic set of images. Curves were first normalized to their respective mean count. The autocorrelation function

\[
A(T) = \frac{1}{T} \int C(t)C(t+T)dt,
\]

where \( t \) is the time, and \( T \) the lag time of the correlation, was then applied to each set of normalized data. This function eliminates the background noise and the nonperiodical events in the defined time interval. The frequency (in contractions per min) and amplitude in the time domain (in percent variation around the mean) of the antral contractions were obtained for each set of dynamic acquisition using Fourier transform analysis

\[
F(w) = \Delta f A(T) \cdot \cos(wT)dt,
\]

where \( w \) is the pulsation frequency. A scintigraphic antral motility index (MI) equal to the frequency multiplied by the amplitude of the antral contractions was also determined. The dominant frequency, corresponding amplitude and MI of the entire antrum was calculated as a mean of the subregions per time interval and the average dominant frequency, corresponding amplitude and MI for the whole gastric emptying course were calculated for each subject.

**Statistical analysis.** All results are expressed as mean ± SEM. Unpaired \( t \) tests were used to compare the T/2 values, the Tlag, the ER and the regional percentages of meal retention, as well as the frequency of antral contractions, corresponding amplitude...
Table 1. Gastric-emptying values for solids and liquids in men and women

<table>
<thead>
<tr>
<th></th>
<th>Solids</th>
<th>Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$T'\bar{2}$ (min)</td>
<td>$T'\bar{2}$ (min)</td>
</tr>
<tr>
<td>Men</td>
<td>52.3 ± 2.9</td>
<td>31.7 ± 2.4</td>
</tr>
<tr>
<td>Women</td>
<td>86.2 ± 5.1*</td>
<td>35.2 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>Tlag (min)</td>
<td>ER (%/min)</td>
</tr>
<tr>
<td>Men</td>
<td>25.2 ± 2.20</td>
<td>2.4 ± 0.10</td>
</tr>
<tr>
<td>Women</td>
<td>43.7 ± 4.7*</td>
<td>1.5 ± 0.1*</td>
</tr>
<tr>
<td></td>
<td>ER (%/min)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.44 ± 0.00</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.55 ± 0.00*</td>
<td></td>
</tr>
</tbody>
</table>

Mean values ± SEM

* $P < 0.05$

and motility indices between men and women. Regression lines were also compared using a student’s $t$ test. All statistical tests were 2-tailed, and differences were evaluated at the 5% level of significance.

**Results**

**Total gastric emptying**

Total gastric emptying of solid test meal was determined in all 31 male and 20 female volunteers (Fig. 1A). Gastric emptying of the solid test meal was significantly slower in women as compared to men. We determined the $T'\bar{2}$, Tlag and ER for solid test meal in all male and female volunteers (Table 1). The $T'\bar{2}$ value of the solid test meal was significantly longer in women as compared to men (86.2 ± 5.1 and 52.2 ± 2.9 min, respectively). The Tlag was significantly longer and the ER was significantly slower in female volunteers (Fig. 2).

Total gastric emptying of liquid test meal was determined in 26 male and 19 female volunteers (Fig. 1B). No significant differences were observed between male and female volunteers. The $T'\bar{2}$ value and ER for liquid test meal are shown in Table 1. No significant differences were observed for these parameters between men and women.
Normal gastric emptying in male and female

**Figure 1.** Total gastric-emptying curves for solids and liquids in male and female volunteers

Solid (A) and liquid (B) meal retention in the total stomach in male and female volunteers. Gastric emptying of solids is significantly slower in women as compared to men. *p < 0.05. Gastric emptying of liquids is not significantly different. (Mean values ± SEM)
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Figure 2. Parameters of gastric emptying

(A) The half-emptying time (T\(\text{1/2}\)) and the lag-phase (Tlag) are significantly longer in women as compared to men (\(P < 0.0001\) and \(P < 0.01\), respectively). (B) The gastric emptying rate is significantly slower in women as compared to men (\(P < 0.001\)).

Compartmental gastric emptying

Regional tracer distribution of solid test meal between the proximal and distal stomach was determined in 12 men and 20 women (Fig. 3). We noted significantly longer tracer retention in the proximal stomach in women and a later occurrence of peak-activity in the distal stomach. The terminal slope of the distal stomach emptying is significantly lower in women as compared to men (\(P < 0.001\)).

Dynamic antral scintigraphy

Frequency. The mean overall dominant antral frequency and corresponding amplitude and the mean dominant antral frequency and corresponding amplitude per time interval were determined in 12 men and 20 women (Table 2). The frequency of the antral contractions remains remarkable stable during gastric emptying with a mean of 3.06 ± 0.06 and 3.07 ± 0.04 contractions per min in male and female volunteers.
Normal gastric emptying in male and female

**Figure 3. Regional gastric emptying curves for solids in male and female volunteers**

Solid meal retention in proximal (A) and distal (B) stomach. There is a significantly higher tracer retention in the proximal stomach and a later occurrence of peak activity in the distal stomach. *P<0.05 (Mean values ± SEM)

This is in concordance with earlier results of Urbain et al.\textsuperscript{14} Neither at the level of the mean overall antral frequency nor at the level of the mean antral frequency per time interval (Fig. 4) could a significant difference be detected between men and women.

**Amplitude.** The overall corresponding amplitude of the antral contractions had a mean value of 15.91% ± 1.59% and 15.04% ± 0.87% in male and female volunteers. Neither at the level of the mean overall antral amplitude nor at the level of the mean antral amplitude per time interval (Fig. 4) could a significant difference be detected.

**Motility index.** The mean overall motility index had a value of 47.86 ± 4.13 and 46.08 ± 2.76 in male and female volunteers. Neither at the level of the mean overall antral motility index nor at the level of the mean antral motility index per time interval (Fig. 4) could a significant difference be detected.
Table 2. Dynamic antral scintigraphy for the solid test meal in men and women: mean overall values

<table>
<thead>
<tr>
<th></th>
<th>Frequency (contr./min)</th>
<th>Amplitude (%)</th>
<th>Motility index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>3.06 ± 0.06</td>
<td>15.91 ± 1.59</td>
<td>47.86 ± 4.13</td>
</tr>
<tr>
<td>Women</td>
<td>3.07 ± 0.04</td>
<td>15.04 ± 0.87</td>
<td>46.08 ± 2.76</td>
</tr>
</tbody>
</table>

Mean values ± SEM

Discussion

Radionuclide gastric emptying studies are widely used for clinical and research purposes. The normal values for these studies are generally based on all-male or mixed populations, because it has been assumed that men and women have identical rates of gastric emptying.\(^2\,\,3\,\,16-19\) Over the last 10 years, however, it has become increasingly evident that women have slower gastric emptying rates for solids\(^20\,\,22\) and possibly for liquids.\(^23\) Since most dyspeptic patients seem to be female, it is of clinical importance to know whether present normal ranges of gastric emptying values can still be used to differentiate between normal and pathological values, or whether separate normal ranges for men and women need to be defined.

In the scintigraphic determination of gastric emptying there are many parameters which can affect the final result. Factors such as meal size, meal composition, subject age and weight and measurement technique are known to influence gastric emptying.\(^15\,\,17\,\,21\,\,26\,\,27\) It is therefore of prime importance that as much as possible standardized conditions are used in performing scintigraphic gastric emptying studies.

In female volunteers “delayed” gastric emptying of solids seems to be related to a prolonged lag phase and slowing of the emptying rate. This phenomenon has also been observed in patients with idiopathic dyspepsia.\(^28\) Furthermore, our observations concur with the findings of another study comparing gastric emptying in men and women.\(^29\) In contrast, we observed no difference in antral motility between male and female...
Normal gastric emptying in male and female

![Diagram showing mean antral frequency, amplitude, and motility index](image)

**Figure 4. Mean antral frequency, amplitude, and motility index**

The mean antral frequency (A), corresponding amplitude (B) and motility index (C) per time interval are not significantly different between men and women. (Mean values ± SEM)

volunteers. With regard to the compartmental gastric emptying curves, we observed prolonged tracer retention in the proximal and distal stomach in female volunteers. This phenomenon has also been demonstrated in patients with diabetes mellitus. Increased retention of solid test meal in the proximal stomach can explain the prolongation of the lag phase in women. In symptomatic and asymptomatic diabetes patients delayed gastric emptying of solids has also been attributed to a prolonged lag phase due to increased proximal retention\textsuperscript{14, 30, 31}. A difference in fundic motor activity is a possible explanation, which should be further assessed. It has been stated that the lag phase calculated by the power exponential function reflects the peak antral filling.\textsuperscript{14} This correlates well with our data, where peak antral filling occurred later in women than in men.

Besides a significantly slower emptying rate for the solid test meal in women, we observed a significantly decreased terminal slope of the distal stomach emptying, without a significant difference in antral motor activity. This is in contrast with delayed gastric emptying in patients with idiopathic dyspepsia or diabetes mellitus, in whom a significantly different antral motility has been observed.\textsuperscript{14, 28} Our observations suggest that antral motility is not a major factor in the gender-based difference in gastric emptying. This latter observation was also made in the study of Hutson et al.,\textsuperscript{21} who assessed antral motility with a multi-lumen perfusion catheter. However, we did observe
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an increase in mean frequency, corresponding amplitude and motility index during the first 20 min as compared to the initial values in both male and female volunteers. This is probably caused by the phenomenon of lag phase and antral filling. Initially, the antrum is almost empty with a low scintigraphic signal, making dynamic evaluation hazardous.

Normal gastric emptying requires optimal coordination of the proximal stomach, antrum, pylorus and duodenum. Different pyloric or proximal small bowel motility might play a role in different gastric emptying of man and women for solids. The amount of chyme emptied per unit of time is determined by the force of the antral contractions, the tone of the proximal stomach and the contractile activity of the pylorus and duodenum.

The fact that we observed no significant difference in gastric emptying of non-caloric liquids suggests that the caloric value of the test meal may play a role in generating this difference, since a difference between gender has been demonstrated in gastric emptying of orange juice as a liquid test meal.

In search for an explanation for the gender related differences in gastric emptying, the possible effect of sex hormones such as progesterone and estradiol was evaluated by comparing emptying rates of pre- and postmenopausal women. Estradiol and progesterone may distinct gastric emptying by a direct effect on gastrointestinal motility. Progesterone may also act indirectly, by decreasing plasma levels of motilin, a gastrointestinal smooth muscle-stimulating hormone. Animal studies showed that sex hormones are responsible for slowing gastrointestinal transit but that absolute levels of hormones are not important as demonstrated in rats. In non-pregnant premenopausal women the effect of the time point in the menstrual cycle on the rate of gastric emptying remains controversial; however this seems not of paramount importance.

Postmenopausal women not taking sex hormone replacement therapy have significantly more rapid gastric emptying with rates similar to men.

The slower gastric emptying in premenopausal women is not related to a decrease in antral motility, although the emptying rate of the antrum is significantly lower. In a 2-compartment model of the stomach the first major difference is situated in the fundus, which might be related to a difference in fundic motor activity. Whether hormones have an effect on fundic motor activity, without affecting antral motility is unclear. It is not
very likely, though, that a different fundal tonus affects the emptying rate of the antrum after peak filling. Other mechanisms such as a decrease in gastric outflow related to a decrease in pyloric relaxation or in antroduodenal coordination could play a role. It is also questionable whether quantitative or qualitative changes in variation of the chemical breakdown of the test meal may differ with gender. The possible role of these mechanisms on gastric emptying should be further assessed in separate male and female subpopulations.

**Conclusion**

Dual-isotope scintigraphy is the gold standard for evaluation of gastric emptying. With the addition of powerful tools such as regional gastric emptying and dynamic antral scintigraphy the test is even more informative without increasing the radiation burden excessively.

We demonstrated that gastric emptying of solids is significantly slower in women as compared to men. In contrast with pathological situations such as idiopathic or diabetes mellitus gastroparesis, where antral motor activity is affected, the antral motor activity does not seem to play a major role in the gender difference. In our opinion, the gastric fundus is also responsible for delaying the gastric emptying in females.

Gastric emptying of a noncaloric liquid test meal did not differ significantly in males and females.

For routine clinical purposes, each nuclear medicine facility should define 2 separate sets of normal gastric emptying reference values for men and premenopausal women. As regards future experimental work, we believe it is of major interest that investigations are carried out separately for men and women. This might clarify some of the contradictions in the literature, possible caused by different ratios of men and women in study protocols.
References


Normal gastric emptying in male and female


