

Biphasic nature of gastric emptying

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SUMMARY The existence of a lag phase during the gastric emptying of solid foods is controversial. It has been hypothesised that among other early events, the stomach requires a period of time to process solid food to particles small enough to be handled as a liquid. At present no standardised curve fitting techniques exist for the characterisation and quantification of the lag phase or the emptying rate of solids and liquids. We have evaluated the ability of a modified power exponential function to define the emptying parameters of two different solid meals. Dual labelled meals were administered to 24 normal volunteers. The subjects received meals consisting of either Tc-99m *in vivo* labelled chicken liver or Tc-99m-egg, which have different densities, and In-111-DTPA in water. The emptying curves were biphasic in nature. For solids, this represented an initial delay in emptying or lag phase followed by an equilibrium emptying phase characterised by a constant rate of emptying. The curves were analysed using a modified power exponential function of the form $y(t) = 1 - (1 - e^{-kt})^\beta$, where $y(t)$ is the fractional meal retention at time t , k is the gastric emptying rate in min^{-1} , and β is the extrapolated y -intercept from the terminal portion of the curve. The length of the lag phase and half-emptying time increased with solid food density (31 ± 8 min and 77.6 ± 11.2 min for egg and 62 ± 16 min and 94.1 ± 14.2 min for chicken liver, respectively). After the lag phase, both solids had similar emptying rates, and these rates were identical to those of the liquids. *In vitro* experiments indicated that the egg meal disintegrated much more rapidly than the chicken liver under mechanical agitation in gastric juice, lending further support to the hypothesis that the initial lag in emptying of solid food is due to the processing of food into particles small enough to pass the pylorus. We conclude that the modified power exponential model permits characterisation of the biphasic nature of gastric emptying allowing for quantification of the lag phase and the rate of emptying for both solids and liquids.

Many studies have indicated that the gastric emptying of solids is biphasic in character.¹⁻⁸ The existence of a lag phase which precedes the gastric emptying of solid food, however, is controversial. In this study we have evaluated a model in which the stomach requires a period of time to process solid food to particles small enough (<1–2 mm in diameter) to pass the pylorus. Dual isotope gastric emptying was carried out on 24 normal volunteers using either Tc-99m-egg sandwich or Tc-99m *in vivo* labelled chicken

liver for the solid meal. If the duration of the solid lag phase depends upon processing of the solid food,^{2,9} then meals which are more difficult to break down – for example, chicken liver, should have a longer lag phase than meals which are easier to digest – for example, eggs.

The gastric emptying data for liquids and both solids were fit to a modified power exponential which could determine the characteristic rate of solid and liquid emptying as well as any delay which preceded the onset of emptying.¹⁰ In addition, these two solid meals were evaluated *in vitro* in gastric juice to determine if there was a difference in digestion between them.

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Methods

SUBJECTS

Twenty four volunteers were recruited for these studies. They consisted of 20 men and four women, with an age range of 21–42 years (mean 27 years). The study of these volunteers was approved by the Human Research Review Committee of Temple University School of Medicine. Written informed consent was obtained from all volunteers before they were studied.

A dual component standard test meal consisting of either Tc-99m-egg sandwich (n=14) or Tc-99m *in vivo* labelled chicken liver (n=10) for the solid and In-111-diethylenetriaminepentaacetic acid (DTPA) in water for the liquid component was administered to the volunteers.¹¹ The egg sandwich was prepared by injecting 18.5 MBq (500 μ Ci) of Tc-99m-sulphur colloid into two beaten raw eggs. The eggs were then cooked until firm in consistency and placed between two slices of white bread toast. This method results in firm binding of Tc-99m sulphur colloid to the eggs.¹¹ The weight of the egg meal was 142 g with a caloric content of 270 calories distributed as 23% protein, 40% fat and 37% carbohydrate. The chicken liver was prepared by injecting 37 MBq (1.0 mCi) of Tc-99m-sulphur colloid into the wing vein of a live chicken. Thirty minutes later, the chicken was slaughtered, and the liver removed and agitated in a water bath for five minutes. The liver was then baked for 20 minutes at 350°. After cooking, the chicken liver was cut into 0.5 cm cubes and added to a can of chicken stew. The weight of the chicken liver meal was 260 g with a caloric content of 243 calories distributed as 26% protein, 38% fat, and 36% carbohydrate. The mean time to eat was 7.5 min with a range of six to nine minutes for the egg meal and eight minutes with a range of seven to 10 minutes for the chicken liver meal. The liquid component consisted of 4.6 MBq (125 μ Ci) of In-111-DTPA in 300 ml water and was administered at the end of the solid meal to each volunteer.

Immediately after ingestion of the dual labelled meal, the subjects were placed supine under a large field of view gamma camera fitted with a medium

energy collimator and interfaced to a nuclear medicine computer system (Medical Data Systems, Ann Arbor, MI). Twenty per cent energy windows were set with peaks set at 140 KeV for Tc-99m and 247 KeV for In-111. Images were obtained for one minute in both energy windows at 15 minute intervals for 150 minutes. The subjects were encouraged to sit upright or walk for the 14 minute intervals between images. The acquired images were stored on magnetic discs for subsequent data analyses.

A manual region of interest corresponding to the stomach was outlined to determine the gastric counts for each image. Correction was made for background, scatter, and radioactive decay.¹¹

For each counting interval, the fractional meal retentions for both solid (Tc-99m) and liquid (In-111) components were determined within the gastric region of interest. The fractional retention was obtained by dividing the decay-corrected gastric counts at each time interval by the maximum (time zero) value.

The fractional meal retention values were analysed using the function $y(t) = 1 - (1 - e^{-kt})^\beta$, where $y(t)$ is the fractional meal retention at time t , k is the gastric emptying rate in min^{-1} , t is the time interval in minutes, and β is the extrapolated y -intercept from the terminal portion of the curve as shown in Figure 1. The unknown parameters k and β are determined by a non-linear least squares algorithm using the measured fractional meal retention, $y(t)$, versus time, t , data as input. This function can be used to fit all the data points and has previously been shown to be useful for biphasic curve analysis.^{12,13} A value of $\beta > 1.0$ indicates an initial delay in emptying while a value of $\beta < 1.0$ indicates an initial rapid emptying. For solids, the initial delay portion of the curve can be characterised by a lag phase index, T_{LAG} , which is numerically equal to $\ln \beta/k$ and is the time in minutes when the second derivative of the function is equal to zero (Figure 1).

A test to determine the digestion of the eggs and chicken liver *in vitro* was carried out. Two tablespoons of each Tc-99m-labelled solid food was chopped into 3 mm cubes and suspended in 25 ml gastric juice from human volunteers. The suspension was

Table Gastric emptying curve analysis with $y(t) = 1 - (1 - e^{-kt})^\beta$

Parameter	Egg meal (n=14)		Chicken liver (n=10)	
	Liquid	Solid	Liquid	Solid
Emptying rate (k)	-0.0164±0.0007	-0.0142±0.0009	-0.0172±0.0010	-0.0155±0.0013
β	0.70±0.04	1.54±0.09	1.02±0.07	2.62±0.34
Lag phase (T_{LAG})	—	31±2 min	—	62±5 min

Results expressed as mean ± SEM (see text for statistical significance of parameter differences).

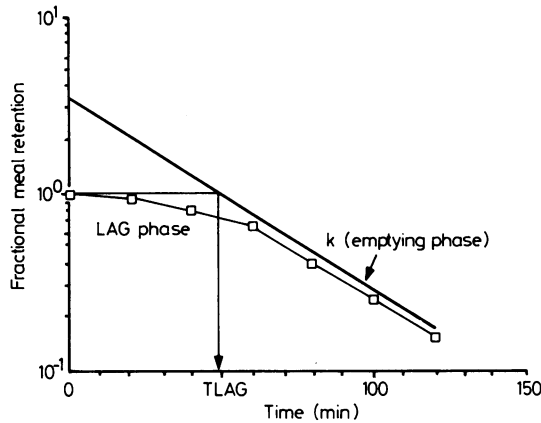


Fig. 1 Fit of the function $y(t)=1-(1-e^{-kt})^\beta$ to a typical solid emptying curve. Graph illustrates the two distinct portions of solid emptying, namely, the lag phase, as indicated by TLAG, and the emptying phase, which is characterised by the emptying rate, k .

then shaken in a 37°C water bath. Initially and at hourly intervals, 5 ml samples were removed and poured through a 5 ml syringe barrel plugged with glass wool. Saline was used to wash the solids remaining on the glass wool filters which only allowed particles finer than 1 mm to pass through. Solids and filtrates were then counted in a well counter.

Results

The mean fractional retention values for both solid meals (Tc-99m-egg sandwich, $n=14$, and Tc-99m *in vivo* chicken liver, $n=10$) and In-111-DTPA in water are shown in Figure 2. For liquids, there is an initial rapid emptying phase followed by a slower linear phase, while for both solids, there is an initial slow phase followed by a more rapid linear phase.

The results of curve fitting with $y(t)=1-(1-e^{-kt})^\beta$ are shown in the Table. There was no significant difference in the slopes for liquid and late solid meal components within or between meals [liquid (egg) ν solid (egg): $0.05 < p < 0.10$; liquid (liver) ν solid (liver): $0.20 < p < 0.40$; liquid (egg) ν liquid (liver): $0.40 < p < 0.60$; solid (egg) ν solid (liver): $0.05 < p < 0.10$]. There was, however, a significantly increased β for solid chicken liver compared with solid egg ($p < 0.01$) indicating a longer initial slow emptying phase (Fig. 2). This is best seen by comparing the lag times (T_{LAG}) for these two solid meals (62 ± 5 min ν 31 ± 2 min for chicken liver and egg, respectively). The differences in β values for liquid (egg) ν solid (egg), liquid (liver) ν solid (liver), and liquid (egg) ν liquid (liver) were also statistically significant ($p < 0.01$). The measured half-emptying times ($t_{1/2}$) were 77.6 ± 11.2 min and 94.1 ± 14.2 min for

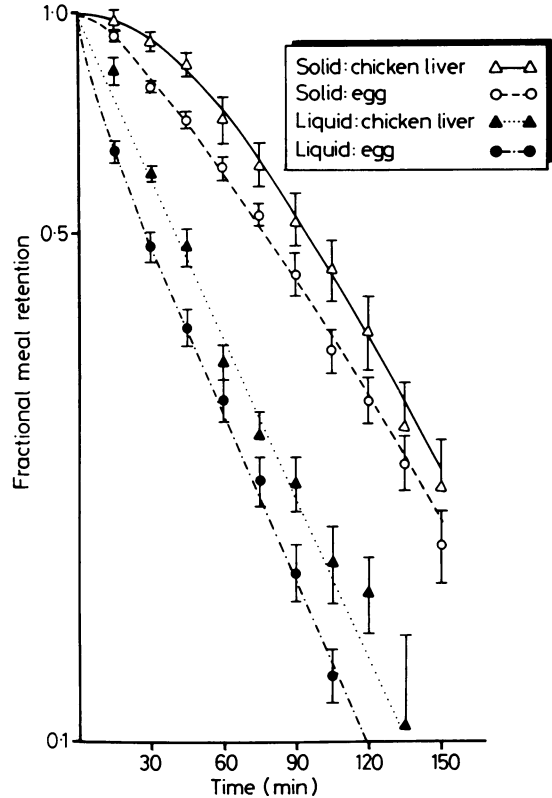


Fig. 2 The mean \pm SEM fractional meal retention values for 24 subjects receiving either Tc-99m-egg sandwich ($n=14$) or Tc-99m *in vivo* labelled chicken liver ($n=10$) and In-111 DTPA water on a semilogarithmic plot.

the egg and chicken liver, respectively, and are significantly different ($p < 0.01$).

The counting of the solid residues and filtrates from the *in vitro* experiments indicated that the egg was broken down to smaller particle sizes more rapidly than the chicken liver. At times 0, 1 h, 2 h, and 3 h the per cent of the food containing particles larger than 1 mm were 99%, 98%, 97%, and 98% for the *in vivo* labelled chicken liver and 98%, 30%, 28%, and 6% for the egg meal.

Discussion

Gastric emptying is a complex process which reflects the digestive work of the stomach. Many studies have supported the concept of biphasic emptying where the stomach requires a certain period of time (lag phase) to process solid foods¹⁻³ before a subsequent equilibrium emptying phase. Differences in lag phase can be the result of variation in: (1) food particle size,² (2) caloric content of the test meal,³ (3) type and amount of solid,^{2,14,15} (4) measurement method-

ology,¹⁶⁻¹⁸ and (5) type of gastroparesis.⁴ The simple measurement of the $t_{1/2}$ emptying time does not characterise either the lag period or reflect a measure of the actual rate of gastric emptying. Thus, there is a need to develop a standardised method for analysis of gastric emptying data.

Gastric emptying data may be analysed by fitting mathematical functions which permit characterisation of the parameters that describe the time course of emptying.¹⁹⁻²¹ These parameters should reflect the physiology of gastric emptying and would permit direct statistical comparisons between normal and abnormal populations. Any method which is used to analyse gastric emptying must clearly reflect the biphasic nature of gastric emptying. It is important to have a standard method to measure the lag phase as certain abnormal patterns of gastric emptying will be manifested mainly by an increase in the lag period. Drugs can be shown to improve gastric emptying primarily by shortening such prolongation of the lag phase.⁴ In this study we have proposed a new method for analysis of gastric emptying data which accurately permits characterisation of the lag phase in minutes, rather than as a non-dimensional number,²⁰ as well as the rate of gastric emptying for liquids or solids.

A controversy, however, over the existence of a lag phase for gastric emptying has resulted from the lack of, or use of, different correction factors for attenuation correction of activity measured during radionuclide studies. Lack of attenuation correction in anteriorly acquired studies has been shown to underestimate the rate of gastric emptying using $t_{1/2}$ criteria only.¹⁶⁻¹⁸ This is because the early posterior to anterior motion (fundus to antrum) of gastric material increases the measured anterior count rates and thus may appear to increase the lag period.

It has been speculated that the lag phase may be purely an artifact created by failure to correct for attenuation¹⁸ but these results may have been related to failure to sample data rapidly enough.²² Proper attenuation correction using a lateral view to correct for differences in the depth of gastric materials,³ the peak-to-scatter ratio,¹⁶ or use of the geometric mean,^{17,18} are the most commonly used methods which have been successful for correcting anterior or posterior only acquired gastric emptying data. A lag phase, however, can be shown in studies even without attenuation correction.⁸

While we recognize that the data used in our current study contain anterior-only acquired data which may tend to overestimate the lag phase, the statistically significant increased lag phase, as calculated by the power exponential function, for the liver meal as compared with the egg meal, reflects the longer time required for the stomach to digest the liver. The difference in digestion between these

two foods, as confirmed by the *in vitro* data may be the result of the increased volume and density of the liver meal. Because certain abnormal patterns of gastric emptying are manifested by an increased lag phase,^{4,10} we believe that use of the proposed power exponential model may be useful as a standardised method of analysis for solid gastric emptying data. In addition, the function allows for solid-liquid discrimination, as no lag phase was observed for liquid emptying of our water meal.

The fact that there is no significant difference in the rates of emptying of the solid and liquid meal components substantiates the theory that once solids have been reduced in size small enough to pass through the pylorus, both the liquids and solids will be emptied at the same rate. This observation – that is, equivalent liquid and solid emptying rates after the solid lag phase, has been previously described.^{3,4,23-25} It must also be noted, however, that the liquids may either be absorbed or clathrated by the solids, causing them to empty at the same rate as solids.

In summary, we have proposed a new method of analysis that permits characterisation of the lag phase and the rate of gastric emptying for both solids and liquids. The length of the lag phase is affected by meal volume and density, while the latter linear phase is independent of these parameters.

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