The Lag Phase of Gastric Emptying: Clinical, Mathematical and In Vitro Studies

Martin L. Nusynowitz and Anthony R. Benedetto

Division of Nuclear Medicine, Department of Radiology, University of Texas Medical Branch, Galveston, Texas

The lag phase of gastric emptying reflects, in large measure, the clinically important milling function of the stomach, but there is little agreement on the best way to acquire, analyze and characterize lag phase data of gastric emptying studies. **Methods:** Twenty normal volunteers were fed a standard ^{99m}Tc-sulfur colloid scrambled egg and toast breakfast and imaging data were acquired at 15-min intervals in both anterior and posterior projections with the subject seated. **Results:** In a significant percentage of the subjects, the stomach count rate rose above the initial count rate, even with geometric mean correction. We attributed the count rate rise to meal self-absorption and conducted mathematical and in vitro experiments, the results of which supported this thesis. Attempts at modeling the data with power exponential fits were unsuccessful in many cases and were complex, nonintuitive and of limited clinical utility. Accordingly, gastric emptying rates were determined by simple linear regression from geometric mean data. The starting index (the time at which the regression line equalled 100%) was calculated to reflect the lag phase. Normal ranges were determined for men and women. **Conclusion:** Our method of test performance is simple, eliminates confounding variables and provides results with intuitive meaning and with direct clinical relevance.

Key Words: gastric emptying; solid meal lag phase; stomach

J Nucl Med 1994; 35:1023–1027

The stomach has at least two mechanical functions in the digestive process: it serves as a mill, triturating food into particles small enough (less than 1–2 mm) to pass through the pyloric valve (*1,2*); and it serves as a pump, propelling gastric contents into the intestine. Studies with radiolabeled solid meals have shown a lag phase (period of minimal or absent emptying) representative of the milling function, followed by linear emptying of gastric contents, the rate of which depends on a variety of factors such as meal size and composition. The duration and characterization of the lag phase is also dependent on a number of factors, such as type of meal, ingested particle size and sampling interval (*3–5*). In order for the lag phase to be a valid representation of gastric milling, test parameters must be designed to stress this function. For example, liquid meals do not show a lag phase, since trituration is unnecessary.

Similarly, labeled liver pate meals, mechanically ground to a fine particle size, reveal a short lag phase and probably do not constitute an adequate test of gastric milling (*6*). We used a scrambled egg and toast sandwich meal because it is readily prepared, palatable and meets other criteria for a valid test meal (*7*); it necessitates considerable gastric milling before emptying can occur and thus allows assessment of both the lag phase and the linear emptying phase.

The purpose of this study is to describe, define and characterize both the lag and emptying phases with an acceptable standard meal in a group of normal adults. We attempted to fit the emptying data to power exponential functions, as has been proposed (*3,4,8*). We found that this was not possible unless data were ignored because a significant fraction of the normal subjects (and also our patient population) demonstrated a transient increase in count rate over the first 30 min or more; simpler descriptors of lag phase and emptying rate were more useful. We theorized that the count rate increase was due to attenuation of radiation by the test meal and, therefore, in addition to our main purpose, we supplemented our clinical studies with mathematical and in vitro experiments to test this hypothesis.

METHODS

Clinical Studies

Studies were performed on 10 normal males (ages 26–32 yr, 68–129 kg, 1.68–1.90 m) and 10 normal pre-menopausal females (ages 20–47 yr, 52–98 kg, 1.58–1.73 m) using a standard 300-g (350 kcal) meal consisting of two large scrambled eggs on two thin slices of white toast, 5 g of margarine and 150 ml of water; 37 MBq of ^{99m}Tc-sulfur colloid was added during preparation of the eggs. The meal was eaten within 10 min, and our subjects were imaged, sitting upright, at 15-min intervals during a 1.5–3-hr observation period, with elapsed time commencing at completion of the meal.

Images were collected with a parallel-hole collimator for 1 min each, first in the anterior projection and then in the posterior projection; total elapsed time was less then 3 min. Stomach region of interest (ROI) data were decay-corrected and used to generate graphs of the fraction of the meal remaining in the stomach as a function of time for the anterior, posterior and derived geometric mean data. Geometric mean was calculated as the square root of the product of the anterior and posterior data at each time point. The graphs exhibited excellent linearity, usually between 30 and 105 min. The data were entered into a linear least-squares fit

Received Apr. 28, 1993; revision accepted Jan. 20, 1994.

For correspondence contact: Martin L. Nusynowitz, MD, Dept. of Radiology, University of Texas Medical Branch, Galveston, TX 77555-07930.

Reprints will not be available.

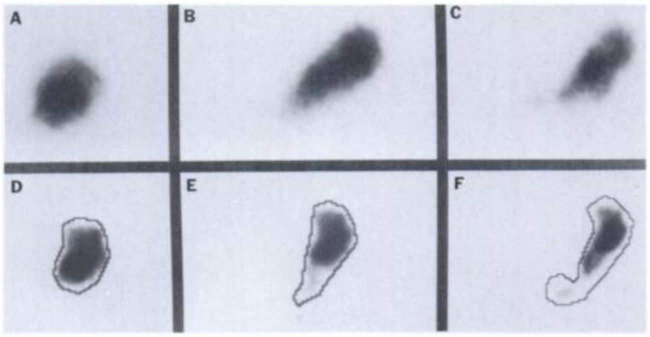

FIGURE 1. Anterior images of the stomach. (A–C) Normal volunteer at 0, 15 and 30 min postingestion showing mild clumping and rapid spreading of the meal. (D–F) Diabetic patient at 0, 30 and 45 min postingestion showing severe clumping and minimal spreading.

routine that calculated the slope of the emptying portion of the curve in units of percentage initial value per minute, the Y-intercept of the line of best fit, and the correlation coefficient, r.

An analysis of covariance was performed to determine whether the slopes between curves were significantly different. The data from males and females were analyzed separately because of the known effect of estrogenization (*9*). We compared the three projections for each individual, then grouped all of the individual values at a given time to obtain an average emptying curve graph for each projection for each gender. A 95% confidence level was used for testing statistical significance of differences.

In addition, the starting index, SI, was calculated for each subject (*10–11*). The SI is the time at which the backprojected line of best fit of the linear portion of the emptying curve intersects the 100% value and is a measure of the lag phase.

Mathematical Studies

Efforts to fit power exponential equations to the patient data (*3,4,8*) were unsuccessful in many cases because the curve rose above the zero-time value of 100% even in the geometric mean count rate curves. Power exponential formulations cannot accommodate values greater than 100%. A rise above 100% can occur in curves obtained from an anterior projection because the meal is moving anteriorly as it progresses through the stomach, but this effect cannot explain the count-rate rise with geometric mean data since they are depth-independent.

To explain geometric mean values greater than 100%, we postulated that attenuation of gamma rays by the meal itself may be responsible for the increase in count rate and for the lengthening of the period of time before linear emptying is evident. The meal is compact during the time immediately after ingestion and gradually spreads as time progresses (Fig. 1). Thus, the surface area of the meal becomes larger while the volume remains relatively constant, so that the area-to-volume ratio increases with time. Sample self-attenuation decreases as the area-to-volume ratio increases (and as the meal thickness decreases). Thus, the count rate observed by a gamma camera would increase with time.

To test this, a mathematical model of the stomach was developed. A 300-g meal was assumed to take the shape of a right circular cylinder of constant 300-cm^3 volume and varying height, creating varying degrees of self-attenuation. Calculations were made of the gamma-ray flux that would impinge on a gamma camera with a parallel-hole collimator for the various source geometries. The cylinders were divided into slices 0.01 mm thick, each containing equal concentrations of activity.

Using various values of the linear attenuation coefficient, μ, to represent the range of gamma-ray energies employed in combined liquid-solid meals, the attenuation of a gamma ray emitted from the center of each slice was calculated along the path from the slice to the gamma camera. The fraction of gamma rays emitted from each slice was summed for all slices within the solid cylinder and then multiplied by the surface area of the slice to obtain the total number of gamma rays reaching the gamma camera.

In Vitro Studies

Solutions of sodium pertechnetate (^{99m}Tc; 37 MBq/ml) and sodium iodide (^{131}I; 7 MBq/ml) were prepared. For each radionuclide alone, 300-ml "meals" were prepared by adding 1-ml aliquots of each solution and 299 ml of distilled water to glass containers having varying diameters to simulate a spreading meal. A gamma camera was positioned above the tallest container and kept at that height for all measurements. A nuclear medicine computer was used to extract data from ROI drawn around each meal.

RESULTS

Clinical Studies

Figure 2 contains curves of grouped normal subject geometric mean data, and Table 1 shows the values for the starting indices and emptying rates for the anterior, posterior and geometric mean data. Note that the slopes for all three data groups ("projections") are not significantly different from one another for either the males or the females, but that the slopes for the females are smaller than those of the males for each of the three projections. This reflects a slower rate of gastric emptying for estrogenized women as compared to men, confirming a previously described finding (*9*). Note also that the starting indices for each of the three projections are significantly different for both the men and the women.

The 15–30-min and 30–45-min columns in Table 2 show the numbers of normal volunteers whose gastric count rate rose above 100% (Fig. 3). Note that count rates for 35% of the subjects rose to over 100% of the initial count rate for the geometric mean data and that all 20 were below 100% by 45 min. The SI values for all normals were also less than 45 min except for one male whose SI was 49 min.

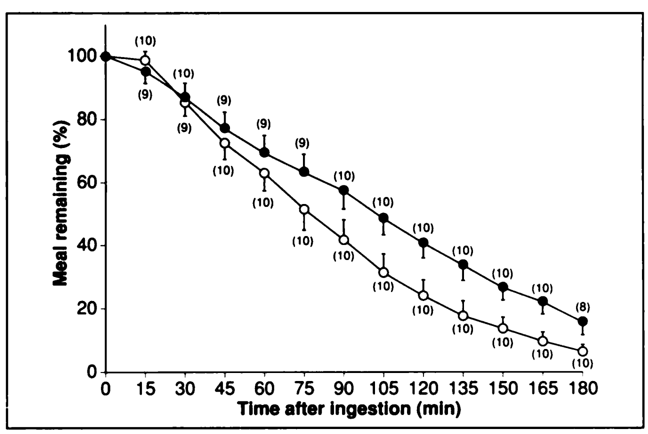

FIGURE 2. Geometric mean gastric emptying data for normal volunteer women (closed circles) and men (open circles). Error bars represent 1 s.e. and ( ) denote number of individuals at each time.

TABLE 1
Starting Index and Gastric Emptying Rate Values for Normal Males and Females

	Males (n = 10)	Females (n = 10)
Starting index (min)*†		
Anterior	30.5 ± 26.3	32.7 ± 38.3
Posterior	−2.0 ± 16.8	−13.1 ± 24.5
Geometric mean	10.8 ± 18.4	4.5 ± 32.5
Gastric emptying rate ($\% \text{ min}^{-1}$)*‡		
Anterior	−0.80 ± 0.25	−0.54 ± 0.07
Posterior	−0.73 ± 0.17	−0.50 ± 0.08
Geometric mean	−0.74 ± 0.19	−0.52 ± 0.05

*All values expressed as mean ± 1 s.d.

†Projections are all significantly different (males, $p < .01$; females, $p < 0.05$); no difference between males and females for a given projection.

‡For males and females, projections are not significantly different; for a given projection, values for males differ from those of women ($p < 0.01$).

As expected, the number of curves above 100% at each of the time periods in Table 2 was greater for the anterior projection and lower for the posterior projection, as compared to the geometric mean data, since the meal proceeds anteriorly as it passes down the stomach.

Mathematical Models

Figure 4 demonstrates the dramatic increase in the gamma-ray flux striking the gamma camera as the projected area of the 300-cm^3 cylindrical meal increased. An area of 41.4 cm^2, where the height of the meal equals its diameter, corresponds to the geometry assumed to exist immediately following ingestion of the meal. The fraction of gamma rays escaping from the cylinder and recorded by the gamma camera at this configuration ranged from about 78% for $\mu = 0.07\ cm^{-1}$ (^{131}I) to about 60% for $\mu = 0.15\ cm^{-1}$ (^{99m}Tc). The effect of self-attenuation was thus somewhat smaller for the smaller attenuation coefficients (higher energy gamma rays), but not small enough to ignore.

In Vitro Data

The results, using glass containers of radioactive solutions, demonstrated increasingly higher count rates for ^{99m}Tc ($\mu = 0.15\ cm^{-1}$) as the projected area of the ^{99m}Tc column increased (Fig. 5). The measured count rates for ^{131}I ($\mu = 0.07\ cm^{-1}$) also increased as the projected area of the column increased, but to a lesser degree, as expected with the higher-energy gamma ray.

TABLE 2
Onset of Linear Gastric Emptying Phase In Normal Volunteers*

	0–15 min	15–30 min	30–45 min	Total
Males	7	2	1	10
Estrogenized females	6	2	2	10

*Number in whom gastric emptying curve dropped below 100% in indicated interval.

DISCUSSION

Datz (*7*) pointed out the need for standardization and scrupulous attention to methodology to minimize variability for valid gastric emptying data, and our methods address each of these issues (Table 3). Whereas our data indicate that slope determination (i.e., emptying rate) is not dependent on projection for a 300-g meal (Table 1), there is no doubt that measurement of the lag phase is highly dependent on projection. We strongly support the position of Datz to use the geometric mean to eliminate the confounding effect of variable patient attenuation resulting from the posterior-to-anterior transit of the labeled meal as it proceeds from the fundus to the antrum.

As our experiments demonstrate, another important reason for using the geometric mean is that the lag-phase curve is confounded by the diminishing self-attenuation of radiation by the food as it spreads and moves toward the antrum. This spreading effect is operative even before significant emptying has occurred, frequently resulting in a rise in the apparent percentage of food remaining in the stomach as compared to the value obtained immediately after meal ingestion. Our thesis that this phenomenon is the cause of the increase, even when using geometric mean corrections, is supported by both our mathematical analysis and our in vitro experiments.

Despite the constraint that measurement of the lag phase cannot exactly reflect the milling process because of the effect of uncontrollable variables such as mastication and fluid secretion by the stomach, the lag phase has clinically significant implications, and its accurate determination is important (*6,12*). However, there is no consensus on the best method of either obtaining the data or quantitatively characterizing the lag phase.

A power-exponential or modified power-exponential fit has been proposed and extensively employed (*3,8,13*), but

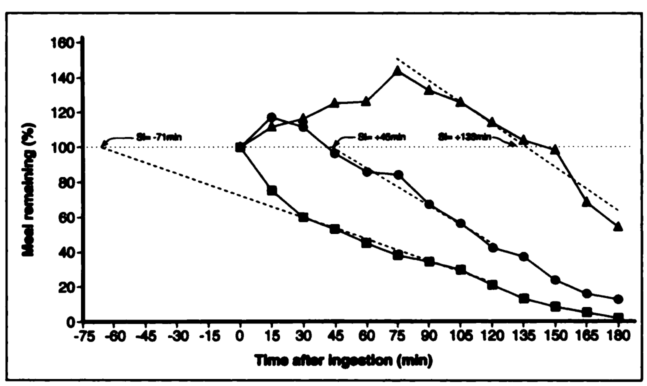

FIGURE 3. Normal and abnormal starting indices in subjects with normal gastric emptying rates. (■) Normal female with rapid onset of emptying (note negative SI); (●) Normal male from Figure 1 with normal onset of emptying; (▲) Diabetic male from Figure 1 with markedly delayed, abnormal onset of emptying.

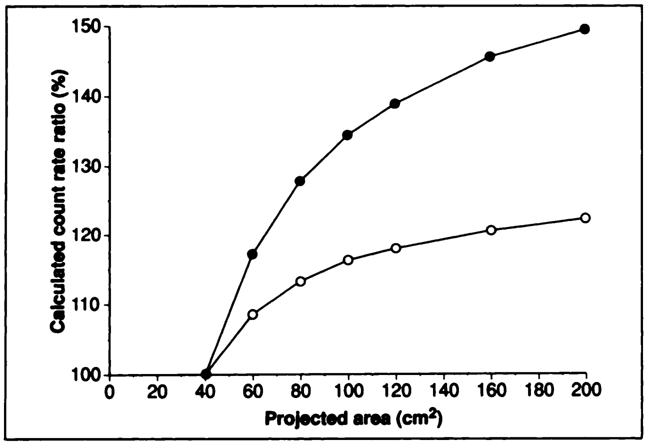

FIGURE 4. Theoretical effect of self-attenuation of gamma rays by the meal as a function of projected area of the meal. Curves are normalized to 40 cm^2, the presumed geometry immediately post-ingestion, and are plotted for linear attenuation coefficients of 0.07 cm^{-1} (○) and 0.15 cm^{-1} (●).

this empirical fitting procedure is neither necessary nor desirable. First, the power exponential procedure results in the derivation of three variables, two to describe the equation of fit and a third to describe the lag phase, none of which represents a readily recognizable physiological parameter (*3*). Second, most authorities agree that the emptying phase for a solid meal is linear, but the power-exponential fit models the data exponentially. Third, because of our observations that in about one-third of normals, and even more commonly in abnormal patients, the emptying curve rises above 100% due to the self-attenuation phenomenon (Figs. 3–5), power exponential fits are impossible to calculate unless values greater than 100% are truncated. Instead, we advocate fitting the linearly-emptying portion of the data with a least-squares regression line and calculating the SI as a measure of lag phase from the slope and Y-intercept.

Describing reproducibly and exactly where gastric emptying starts is impossible from inspection of the curve, but the starting index addresses this problem nicely. Simply

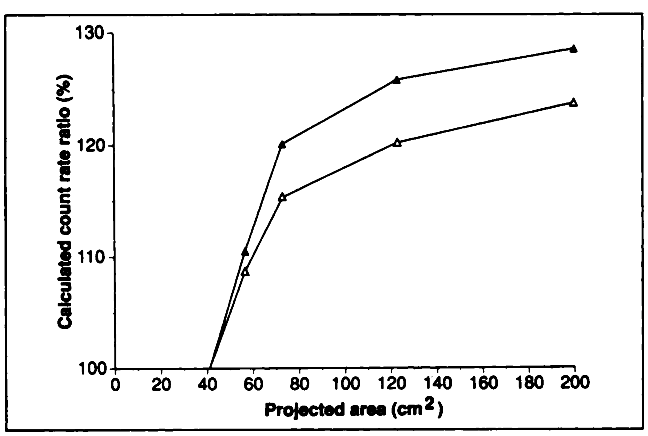

FIGURE 5. Experimentally measured effect of self-attenuation of gamma rays as a function of projected area. Curves are normalized to 40 cm^2 and are presented for ^{99m}Tc (▲) and for ^{131}I (△).

TABLE 3
Desirable and Actual Technical Parameters for Radionuclide Gastric Emptying Studies

Desirable*	Actual
Gastric emptying marker	Food
Type of food	Solid phase egg meal
Particle size	Large (> 5 mm)
Meal calorie content	350 kcal
Meal weight	300 g
Stability of tag	Excellent
Radiopharmaceutical	^{99m}Tc-sulfur colloid
Patient position and movement	Sitting; no walking
Imaging interval	15-min images to 120–180 min
Patient motion during acquisition	None
Decay correction	Used
Dual-radioisotope crosstalk correction	Single radioisotope
Attenuation/geometric effects	Geometric mean
Time of day	Morning
Sex/sex hormone effects	Separate normal values
Stress effects	Quiet room

*Factors this column from Datz (*7*).

put, the SI is the time at which the backprojected regression line of emptying equals 100% (Fig. 3). The technique described herein relates the starting index to the concept of time elapsed before linear emptying is established. Note that if the lag phase is short, the backprojected line of fit may result in a negative starting index (Fig. 3). Since all normal curves dropped below the 100% point by 45 min, normal and abnormal lag phase may be defined in this alternative, less mathematical manner.

Elashoff et al. (*8*) outlined a set of characteristics for the mathematical analysis of gastric emptying data, including that: "The curve should provide a good fit to the data points observed . . ." over a wide range of conditions. The individual regression coefficients for our 20 normal volunteers were all greater than 0.96, demonstrating a superb fit for a linear model. Similar linearity was observed in our patient population. This technique not only has the advantage of simplicity, but it also relates the slope of emptying to the readily comprehensible physiologic parameters of constant linear emptying rate or of grams per minute leaving the stomach. For example, our geometric mean emptying rate for males of 0.74% min^{-1} corresponds to 2.2 g min^{-1} (0.74% min^{-1} × 300 g-meal), which is similar in magnitude to values reported by Moore et al. (*14*).

CONCLUSION

If the emptying rate was sufficient to distinguish normal from abnormal gastric function, data obtained from either the anterior or posterior projections would suffice, since the slopes of the emptying curves are essentially identical. However, because the lag phase is an important parameter of gastric function that largely reflects milling, its accurate characterization is essential, and the use of geometric mean data is mandatory. We have found an initial rise in gastric count rate following the zero-time (100%) value in a large percentage of both normal subjects and in our patients. This elevation may persist for up to 45 min in normal subjects, after which time the linear emptying phase supervenes. Power exponential fits have been proposed to characterize the gastric emptying curve, but they suffer from drawbacks compared to a straight line fit. A straight line fit to the emptying phase data is both readily performed and understandable, has high correlation coefficients and is easily translatable into physiologic meaning: percentage of meal or mass of food emptied per minute. In addition, it allows for calculation of the starting index (a measure of the lag phase), the time at which the fitted regression line of emptying crosses the 100% count rate line. A starting index greater than 45 min is considered abnormally prolonged and thus indicative of a milling-phase disorder.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the generous assistance of John R. Mathias, MD, Division of Gastroenterology, Department of Internal Medicine, in the recruitment of the normal volunteers. Partial funding for imaging of the normal volunteers was furnished by Glaxo Pharmaceuticals.

REFERENCES

1. Meyer JH, Ohashi H, John D, Thomson JB. Size of liver particles emptied from the human stomach. *Gastroenterology* 1981;80:1489–1496.
2. Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 1984;86:1592–1610.
3. Siegel JA, Urbain J-L, Adler LP, et al. Biphasic nature of gastric emptying. *Gut* 1988;29:85–89.
4. Urbain J-LC, Siegel JA, Charkes ND, Maurer AH, Malmud LS, Fisher RS. The two-component stomach: effects of meal particle size on fundal and antral emptying. *Eur J Nucl Med* 1989;15:254–259.
5. Christian PE, Datz FL, Moore JG. Confirmation of short solid food lag phase by continuous monitoring of gastric emptying. *J Nucl Med* 1991;32: 1349–1352.
6. Maurer AH, Knight LC, Krevsky B. Proper definitions for lag phase in gastric emptying of solid foods [Letter]. *J Nucl Med* 1992;33:466–467.
7. Datz FL. Considerations for accurately measuring gastric emptying [Editorial]. *J Nucl Med* 1991;32:881–884.
8. Elashoff JD, Reedy TJ, Meyer JH. Analysis of gastric emptying data. *Gastroenterology* 1982;83:1306–1312.
9. Datz FL, Christian PE, Moore J. Gender-related differences in gastric emptying. *J Nucl Med* 1987;28:1204–1207.
10. Hunt JN, Spurrell WR. The pattern of emptying of the human stomach. *J Physiol* 1951;113:157–168.
11. Soergel KH, Palmer DP, Loo FD, Wood CM. Abnormal gastric emptying in diabetics and the effects of metoclopramide [Abstract]. *Gastroenterology* 1980;78:1265.
12. Horwitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJC. Acute and chronic effects of domperiodone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985;30:1–9.
13. Yung BCK, Sostre S. Lag phase in solid gastric emptying: comparison of quantification by physiological and mathematical definitions. *J Nucl Med* 1993;34:1701–1705.
14. Moore JG, Christian PE, Coleman RE. Gastric emptying of varying meal weight and composition in man: evaluation by dual liquid- and solid-phase isotopic method. *Dig Dis Sci* 1981;26:16–22.