Lag Phase in Solid Gastric Emptying: Comparison of Quantification by Physiological and Mathematical Definitions

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Lag phase is considered an important parameter of solid gastric emptying studies. However, different methodologies with their own normal values and physiologic implications are advocated for lag phase measurements. We applied both physiologic and mathematic approaches to quantify lag phases from identical image data sets for direct comparison of these two approaches. Gastric emptying studies were performed on 22 patients using a standard solid meal to calculate the lag phase in each using three different methods: (1) visual analysis to determine time when activity first appeared in the duodenum (LagPh); (2) time-activity curves to determine time of 2% decrease from peak stomach activity (LagCu); and (3) a mathematical definition using the modified power exponential method (TLAG). In addition, time of peak antral activity (AntPk) was calculated. The values for LagPh and LagCu were very similar (mean: 14.6 versus 15.2 min) and correlated well with each other (r = 0.89). TLAG using the power exponential showed different values (mean: 34.7 min) and correlated well only with AntPk (mean: 35.1 min; r = 0.92). We conclude that LagPh and LagCu estimate the time of onset of gastric emptying; the time when the smaller particles in the meal (<1–2 mm) begin to leave the stomach (onset of variable emptying phase). On the other hand, TLAG and AntPk estimate total trituration time (time for most of meal to be processed) and signal the beginning of the constant gastric emptying phase.

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Based on the concept of different roles played by proximal and distal stomach, the biphasic nature of solid gastric emptying has been well recognized both in animals (*1*) and humans (*2*). The initial lag phase is an important parameter in studying diabetic gastroparesis and is used as an indicator of drug effects on this condition (*3*). While there is little doubt about the existence and physiologic importance of lag phase measurements, the best method for scintigraphic quantification is far from clear.

A wide range of lag phase values (Table 1) obtained from normal subjects is reported in the literature (*4–12*). Lag phase can be estimated visually from image analysis (*6,7,11*), analysis of time-activity curves (*7,8,10*) or mathematical methods using modified exponential curve-fitting according to the function $y(t) = [1 - (1 - e^{-kt})^{\beta}]$ (*4,5,9,12*). These previous studies used solid meals that differed in composition, particle size, caloric content and ways of ingestion with some meals being swallowed without chewing (*9*). Since lag phase has been shown to be affected by particle size (*5,9*) and caloric content (*8,11*), the numerical lag phases reported in these studies cannot be compared directly.

In general, the lag phase obtained from curve-fitting tends to be longer than those by image or time-activity curve analysis. The group advocating exponential curve-fitting believed that the lag phase reported with image or curve analysis (*7*) was falsely short. This was because some radiolabeled particles were so small (2 mm) that no trituration was needed, leading to rapid emptying from the stomach (*13*). While citing data to show that their solid meal was as good as in vivo-labeled chicken liver, the group utilizing imaging and curve analysis methods argued that using a larger particle size and higher caloric content solid meal, as well as swallowing the meal without chewing (*9*) were the actual reasons for prolonged lag phase reported by exponential fitting (*13*). Moreover, the intermittent imaging technique used by the former group to obtain geometric mean (GM) data suffered loss of temporal resolution, and might miss a very short lag phase (*7*). Apart from these methodological differences, various authors have attached different physiologic meanings to the parameters they measured.

Siegel et al. interpreted TLAG as the time required to triturate food, i.e., to break it down into small particles (<1–2 mm) before passing into the pylorus (*5*). This study and a later study by Urbain et al. (*9*) showing that increasing food particle size led to TLAG prolongation and the fact that TLAG is temporally related to peak antral activity further support the concept that TLAG does measure total trituration time. No published studies have directly compared the different approaches to lag phase quantification to investigate the actual magnitude of difference or possible correlations.

To address these issues, we studied patients with con-

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TABLE 1
Representative Studies on Lag Phase Measurement for Solid Gastric Emptying in Normal Subjects

Authors	Solid meal	Particle size	Calories	Quantitation	Lag phase
Collins PJ 1983	chicken liver/ ground beef	—	270	Curve visual	21 ± 2
Siegel JA 1988	egg sandwich/	—	270	Curve fit	31 ± 2
	chicken liver/ beef stew	0.5 cm	243	Curve fit	62 ± 5
Urbain JL 1989	eggs/regular toast	homogen.	318	Curve fit	29 ± 19
		2.5 mm		Curve fit	55 ± 26
		5.0 mm		Curve fit	64 ± 24
Urbain JL 1990	scrambled egg	—	231	Curve fit	28.9 ± 4.4
Maurer A 1991	beaten eggs/ toast bread	— —	270	Curve fit	31.0 ± 7.5
Christian P 1991	canned liver pate/beef stew/orange juice	2–5 mm	208	Curve visual	8.3 ± 3.11
				2% decrease	10.3 ± 3.16
				Image visual	7.4 ± 3.83
Collins PJ 1991	chicken liver	—	270	Image visual	37
Ziessman H 1992	egg sandwich	—	—	5% decrease	15 ± 8

tinuous left anterior oblique (LAO) imaging. Lag phases were calculated both by imaging and mathematical approaches using an identical radiolabeled solid meal. Continuous imaging provided the ideal temporal resolution for a mathematical approach to catch the lag phase even if it was very short. In this way, the true relationship or difference between emptying onset and TLAG under identical investigatory conditions can be elucidated. The hypothesis that TLAG corresponds to peak time of antral radioactivity (*9*) was also tested.

MATERIALS AND METHODS

Patient Population

Patients with gastric symptoms referred for solid gastric emptying studies from March to October 1992 were analyzed. Exclusion criteria included history of prior stomach or duodenal surgery, gross retention of food and flat emptying curves. Twenty-two patients (age 25 to 80 yr; 50.5 ± 15.8 yr; 8 males and 14 females) with either normal or mildly abnormal gastric emptying (between 2 and 5 s.d. from the normal mean $T_{1/2}$) were included in the study. In our institution, using the same solid meal and imaging technique, the normal solid gastric emptying $T_{1/2}$ is 90 ± 15 min.

Scintigraphic Technique

After an overnight fast, the patient was instructed to ingest a solid meal consisting of two scrambled eggs (195 calories) labeled with 0.5 mCi (18.5 MBq) of ^{99m}Tc-sulphur colloid, ingested over 5 min, followed by 200 ml of water. Immediately after, and with the patient lying in a semi-supine position, continuous 45° LAO imaging was performed at 1 min/frame for 2 hr, using a gamma camera with computer interface (GE Starcam 3000XRT, GE Medical Systems, Milwaukee, WI) and low-energy, general-purpose collimator, in a 128 × 128 matrix.

Regions of interest (ROIs) were placed on the entire stomach and distal stomach (antrum). Time-activity curves were generated and corrected for decay (Fig. 1). The following parameters were computed:

LagCu: Lag phase was measured as time of 2% decrease from peak activity on the whole stomach curve normalized to peak radioactivity (LagCu).

TLAG: The stomach curve was normalized to peak activity and fitted to a modified power exponential function: $y(t) = 100[1 - (1 - e^{-kt})^{\beta}]$ using BMDP version PC90, AR program. TLAG was calculated as ln β/k (*5*).

AntPk: Peak time of the antral time-activity curve was read by computer (AntPk).

LagPh: The time at which radioactivity first appeared in duodenum (LagPh) was estimated visually from the 120 one-minute frames displayed on films (Fig. 2).

Statistic analysis: Paired t-test and linear regression analysis were performed on these four parameters using BMDP statistic package to study the differences and correlations. A p-value of < 0.05 was taken as significant.

RESULTS

Values of LagPh, LagCu, TLAG and AntPk, $T_{1/2}$ for all patients and their means ± s.d. are listed in Table 2. The R^2 values which measure the goodness of powered exponential curve-fitting (*14*) are also provided next to each TLAG value. Results of t-test and linear regressions are listed in Table 3.

There was good agreement on the lag phases measured either by curve reading (LagCu, 14.6 ± 10.6 min) or image interpretation (LagPh, 15.2 ± 9.3 min) (r = 0.89). They were significantly shorter and showed very poor correlations with TLAG (r = 0.10). On the other hand, TLAG did correspond to peak of antral activity (AntPk) (r = 0.92).

DISCUSSION

Although it is well accepted that lag phase is an important indicator of gastric emptying function, the best way of quantification is controversial (*13*). Using the physiological definition, normal lag phase as measured by appearance of detectable proximal small intestine activity can be in the range of 8–15 min (*7,10*). TLAG by mathematical definition typically measured 31 min (*4,5*). Some authors believed that TLAG measured trituration time (*5,9*) and it is apparent, by definition, that TLAG can be longer than the onset of gastric emptying. Even so, it remains to be determined whether the numerical differences reported in the literature are attributable to physiological reasons or to technical reasons, such as differing caloric content, particle size and composition of solid meals, as well as imaging protocol. Intermittent imaging at 10–15-min intervals employed by the group favoring mathematical definition made it difficult to obtain values shorter than 10 min.

We tackled this controversy by simultaneously measuring lag phase by both physiological and mathematical models under identical imaging conditions and using the same solid meal. With a single-head camera, LAO projection provides the best setting to measure gastric emptying onset from continuous 1-min frames. Optimal visualization of

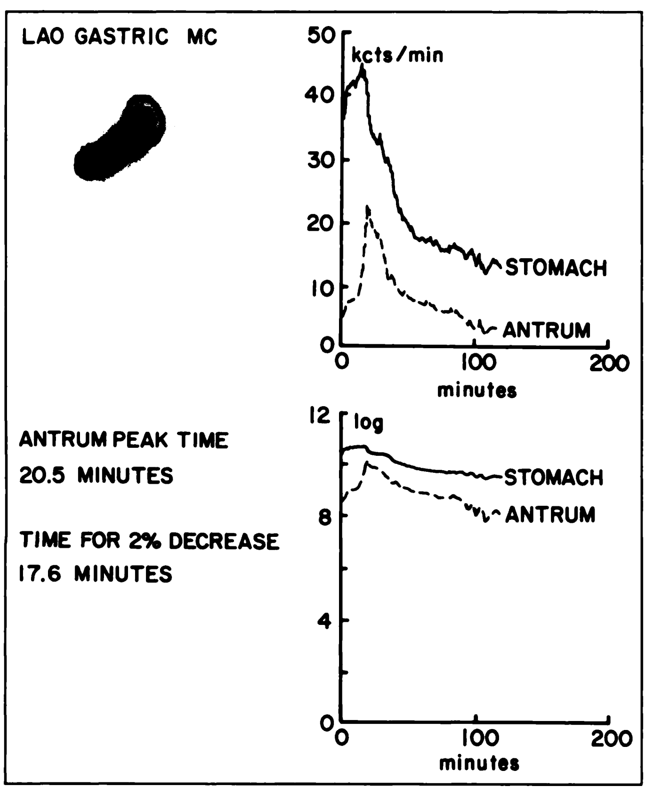

FIGURE 1. LAO stomach image with ROIs and time activity curves.

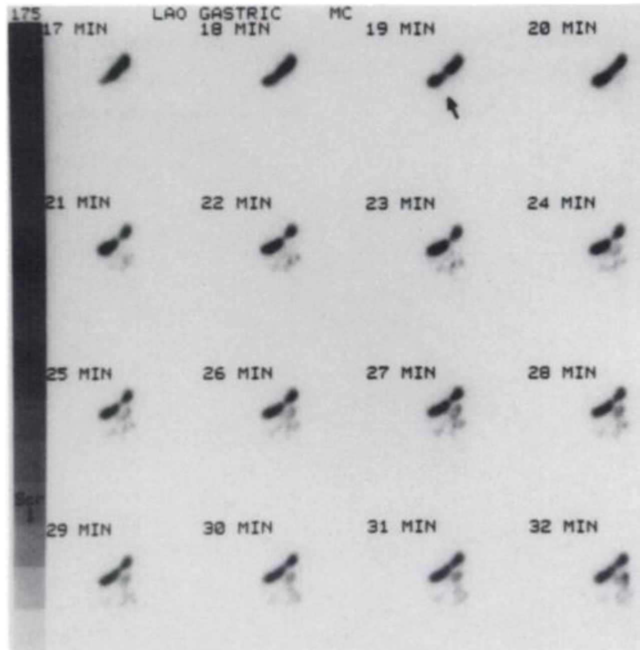

FIGURE 2. Display of 1-min frames for visual identification of lag phase in LAO projection.

radioactivity transit from fundus to antrum allows accurate ROI placement to generate reliable time-activity curves with high temporal resolution. This greatly facilitates computer reading of important time points such as a 2% drop in gastric activity (LagCu) and antral peak time (AntPk). In addition, more data points are available for accurate curve fitting to detect lag phases of less than 10 min than with the intermittent imaging method. Most importantly, LAO has been shown to approximate GM well enough to correct for attenuation changes (*4,15,16*).

Lag phases obtained according to physiological definition, namely, LagPh and LagCu had similar values, and also fell within the ranges reported in literature. On the other hand, TLAG by mathematical definition was significantly longer. The mean values were close to those previously reported using the modified exponential curve-fitting algorithm. This demonstrated that TLAG was actually longer than the time taken for radioactivity to enter the duodenum. The difference is real and cannot be attributed to solid meal variation or imaging techniques. TLAG by LAO method was shown to be significantly longer than that by GM method in one study (*4*), but not confirmed by a later study (*10*). Anyway, the differences between TLAG and LagPh or LagCu in our study and in published series are too big to be merely due to data acquisition differences. The poor correlation between TLAG and LagPh strongly suggests that they bear different physiological meaning instead of just over- or under-estimating one another.

According to Urbain, variable emptying of solids may occur during this first phase of gastric emptying identified by the power exponential function. That is, small particles may empty during this phase while the larger particles are still being broken down. TLAG marks the time at which

TABLE 2
Quantified Gastric Emptying Parameters of All Patients

Patient no.	Age	LagPh	LagCu	TLAG	R^2	AntPk	$T_{1/2}$
1	42	1	1	0	0.9	0	70.9
2	66	16	20.5	33	0.95	32.5	101.6
3	49	14	17.6	42	0.94	26.5	73.1
4	80	4	6	47.5	0.93	28.5	56.2
5	57	15	17.6	37.7	0.85	44.5	74
6	66	8	6	8.2	0.96	28.5	36
7	46	11	6	41.8	0.98	36.5	77.6
8	52	17	11.8	11.5	0.89	12.5	93
9	40	7	6	1.3	0.99	0	65
10	72	13	9	2.2	0.9	9.5	89.9
11	43	3	17.6	40.5	0.95	37.5	56.5
12	62	20	20.5	23.9	0.93	24.5	35.6
13	25	6	8	62.5	0.93	58.5	163.4
14	35	35	30	52.1	0.96	41.5	96.4
15	34	44	35	47.5	0.96	39.5	80.2
16	45	5	6	87	0.93	84.5	109
17	52	15	20	88.7	0.92	81.5	112
18	31	20	23.5	42.5	0.99	56.5	95.8
19	30	25	26.5	30	0.85	31.5	75
20	42	19	17.6	5.5	0.92	20.5	70.9
21	68	20	23.5	30	0.92	42.5	107
22	75	3	5	27.5	0.99	34.5	46.2
mean	50.6	14.6	15.2	34.7		35.1	81.2
s.d.	15.8	10.6	9.3	24.8		21.8	28.8

the major part of trituration ends and constant emptying begins (*9*).

Based on this concept, gastric emptying starts during the variable phase, before the end of TLAG as measured by curve fitting. TLAG represents the time required for trituration of the major portion of the meal, corresponds to the time of maximal antral activity and signals the beginning of constant gastric emptying of solids. For this reason, it is not surprising that values for TLAG are longer than values for gastric emptying onset.

In summary, we found that lag phase measurements by visual and time-activity curve methods were very similar to each other, but significantly shorter than TLAG measured by the power exponential method. LagPh and LagCu probably represent onset of gastric emptying which occur during the variable emptying phase of solids. On the other hand, TLAG correlated well with time of peak antral activity and probably represents total trituration time and onset of the constant emptying phase.

Mathematically derived (TLAG) and physiologically defined measures of lag phase (LagPh and LagCu) are not different because of variations in methodology. They probably represent different physiologic parameters. However, it was not the intention of this study to investigate the actual physiologic processes measured by these parameters, or their variations with different particle size and meal composition.

This represented an initial step to confirm the major numerical differences between physiologically and mathematically defined lag phases. Future studies should evaluate the clinical utility of these parameters. We advocate quantification of both onset of gastric emptying (LagPh or LagCu) and total trituration time (TLAG) using either LAO or GM methodology in different gastric disorders. We may then be able to determine which is more sensitive to pathologic changes and effects of therapeutic interventions, so as to choose the better approach in clinical studies.

TABLE 3
Results of t-test and Linear Regression Analysis on Gastric Emptying Parameters

	LagCu	TLAG	AntPk
LagPh	t-test: not significant r = 0.89 $p < 0.0001$	t-test: significant r = 0.10 p = 0.66	t-test: significant r = 0.09 p = 0.69
LagCu		t-test: significant r = 0.24 p = 0.26	t-test: significant r = 0.25 p = 0.25
TLAG			t-test: not significant r = 0.92 $p < 0.0001$

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