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## Optimizing Analysis of Stable Isotope Breath Tests to Estimate Gastric Emptying of Solids

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### Abstract

Breath tests using  $^{13}\text{C}$ -substrates have been proposed for the measurement of gastric emptying (GE). The mathematical analysis of the breath  $^{13}\text{CO}_2$  excretion that most accurately predicts GE  $t_{1/2}$  from simultaneous scintigraphy is unresolved.

**Aim**—To compare 5 mathematical methods to estimate GE  $t_{1/2}$  by breath test (BT) with  $t_{1/2}$  from simultaneous scintigraphy.

**Methods**—Data acquired from a dual-labeled solid-liquid meal containing  $^{99\text{m}}\text{Tc}$  sulfur colloid and  $^{13}\text{C}$ -*Spirulina platensis* from 57 healthy volunteers were used to compare 4 mathematical methods reported in the literature (Ghoos method; generalized linear regression [Viramontes]; linear regression [Szarka]; Wagner-Nelson method) and the total cumulative breath  $^{13}\text{CO}_2$  excretion with  $\geq 12$  breath samples collected over at least 4 hours. The concordance correlation coefficient (CCC) for the  $t_{1/2}$  results obtained with each method using breath test data was compared with the results obtained with scintigraphy.

**Results**—The linear regression and generalized linear regression methods used 5 samples at 45, 90, 120, 150 and 180 minutes. All methods, except for the Wagner-Nelson method, resulted in mean GE  $t_{1/2}$  that approximated  $t_{1/2}$  obtained with scintigraphy. The highest CCC was observed with the linear regression method. Simple cumulative excretion of breath  $^{13}\text{CO}_2$  provides a better CCC than the Ghoos method.

**Conclusion**—The linear regression and generalized linear regression methods (which also require relatively few breath samples) provide the most accurate analyses of breath  $^{13}\text{CO}_2$  excretion in stable isotope GEBT.

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## Keywords

scintigraphy; spirulina

## INTRODUCTION

Scintigraphy is the accepted gold standard for measurement of gastric emptying of solids and, worldwide, it is the most commonly used method; consensus protocols for measurement of gastric emptying have been recently published (1). However, scintigraphy is not generally available, and involves radiation exposure, precluding use in pregnant patients and healthy children. Thus, breath tests using  $^{13}\text{C}$ -substrates ( $^{13}\text{C}$ -octanoic acid breath test,  $^{13}\text{C}$ -OABT, or the edible  $^{13}\text{C}$ -enriched blue-green alga, *Spirulina platensis*) have been proposed for the measurement of gastric emptying. These substrates are rapidly absorbed in the proximal small intestine, metabolized in the liver with the production of  $^{13}\text{CO}_2$  which is exhaled rapidly with low interindividual variability (2). Thus,  $^{13}\text{CO}_2$  exhalation reflects gastric emptying of nutrients (2).

Several of the breath test methods, using different mathematical models to analyze the breath test, have been compared to results obtained with simultaneous scintigraphy (2–7). The optimal mathematical analysis for the interpretation of these breath test metrics is still unclear. Ghooos et al. developed the original nonlinear regression or Ghooos model (2). In prior studies from our laboratory, we had noted that the results using this model differed significantly from the results obtained by simultaneous scintigraphy, and that the accuracy of the test could not be enhanced by increasing the duration of breath collection (3). In other studies, we noted that breath  $^{13}\text{CO}_2$  excretion continued to increase after the radioisotope had been shown to have emptied from the stomach during simultaneous scintigraphy (4,5). By way of contrast, the analysis proposed by Ghooos et al. (2) requires a steady state in  $^{13}\text{CO}_2$  excretion to have been achieved by the end of the breath collection. Our experience was that the parameter  $m$ , which reflects this portion of the breath  $^{13}\text{CO}_2$  excretion curve, was not constant, and in several instances exceeded 100% of the given dose (4,5). This overestimation of the parameter  $m$  led to erratic performance of the mathematical model relative to the gold standard.

Therefore, an alternative approach was developed in which the analysis was based on a minimum number of breath samples at pre-specified times during the 3 hour postprandial period to mathematically predict the gastric emptying  $T_{\text{lag}}$  and  $T_{1/2}$  measured by simultaneous scintigraphy (4,5). Other mathematical methods have also been proposed in the literature.

The aim of the current study was to compare 5 mathematical methods to estimate gastric emptying results, and to compare the results with those obtained with simultaneous scintigraphy. In order to evaluate the performance of the mathematical models in a broad range of gastric emptying rates, we used pharmacological approaches to accelerate or retard gastric emptying.

## METHODS

### Study Design

This is a single cohort study of data obtained in 57 healthy volunteers. Scintigraphic and breath test data using a dual-labeled, solid-liquid meal of egg whites, whole wheat bread and skimmed milk containing  $^{99\text{m}}\text{Tc}$  sulfur colloid and  $^{13}\text{C}$ -*Spirulina platensis* were used to compare 4 mathematical methods reported in the literature and a fifth approach based on the cumulative excretion of  $^{13}\text{CO}_2$  over 4 hours. Details of participants and methods are published elsewhere (6).

## Subjects and Conduct of Gastric Emptying Tests

The healthy volunteers (26 males), aged 18–56 years (mean 34, SD 9.7 years), and body mass index median 24.9 kg/m<sup>2</sup> (range 18.7±41.9), were recruited by public advertisement. Written informed consent was obtained before participation in the protocol, which was approved by the Institutional Review Board and the Radiation Control Committee of the Mayo Clinic. <sup>13</sup>C<sub>2</sub> breath test was conducted using <sup>13</sup>C–*S. platensis*, an edible blue-green alga that contains 50±60% protein, 30% starch, and 10% lipid. When metabolized, the proteins, carbohydrates and lipids of the *S. platensis* give rise to respiratory CO<sub>2</sub> that is enriched in <sup>13</sup>C. The test meal consisted of eggs dosed with 200 mg of <sup>13</sup>C–*S. platensis* (AB Diagnostics, Inc., Houston, TX, USA) and 0.5 mCi <sup>99m</sup>Tc-sulphur colloid. The egg whites were mixed with 0.5 mCi <sup>99m</sup>Tc-sulfur colloid.

After an overnight fast, anterior and posterior scintiscans were obtained using a large field of view camera with the patient standing. Imaging began at the start of the test meal, and scans were obtained every 15 minutes for the first 2 hours and every 30 minutes for the next 3 hours (total 5 hours). End-tidal breath samples were obtained before the meal and at the same times as the Ghos camera images. <sup>13</sup>C<sub>2</sub> breath content was determined in a centralized laboratory by isotope ratio mass spectrometry (8,9).

Scintigraphic gastric emptying was summarized using a power exponential model (10).  $\text{prop}_t = [\exp -(\kappa t)^\beta]$  where  $\text{prop}_t$  is the proportion remaining in the stomach at time  $t$ . The index  $\kappa$  represents the instantaneous slope of the curve;  $\beta$  is an index for the shape of the curve ( $\beta = 1$  implies a simple exponential emptying model as occurs with liquid emptying). The parameters  $\kappa$  and  $\beta$  were estimated using the nonlinear least squares (NLIN) procedure in the SAS software package (11). The gastric half-emptying times ( $t_{1/2}$ ) were derived after estimating  $\kappa$  and  $\beta$  for each subject, and solving the following equation for  $t_p = (1/\kappa) * [\text{Log}((1/p))]^{(1/\beta)}$ , where  $p=0.5$ .

The <sup>13</sup>C enrichment determined by isotope ratio mass spectrometry was expressed as the delta per mL difference between the <sup>13</sup>CO<sub>2</sub>/<sup>12</sup>CO<sub>2</sub> ratio of the sample and the standard. To calculate the quantity of <sup>13</sup>C appearing in breath per unit time, delta over baseline (DOB) was used: <sup>13</sup>C<sub>μmol/L/min</sub> = DOB X 0.0112372 X CO<sub>2</sub> production, where 0.0112372 is the isotopic abundance of the limestone standard, Pee Dee Belemnite, and CO<sub>2</sub> production was corrected for age, sex, height and weight using the algorithms of Schofield et al. (12).

## Atropine and Erythromycin Dosing to Mimic Delayed and Accelerated Gastric Emptying

Subjects were randomized to a total dose of intravenous atropine (0.01 or 0.02 mg/kg) or intravenous erythromycin (2.0 or 3.0 mg/kg), or no treatment, and the bolus was given immediately prior to meal ingestion, and infusion continued over 50 minutes as previously described (6). These infusions provided gastric emptying rates to simulate a spectrum from dumping syndrome to severe gastroparesis. As published previously (6), there were no age, height, weight, BMI (by ANOVA) or gender (by  $\chi^2$ ) differences among the erythromycin (n=10), control (n=33), and atropine (n=14) groups.

## Mathematical Methods Used for Analysis of Breath <sup>13</sup>C<sub>2</sub> Excretion Curves

Five different methods were investigated to compare their ability to provide estimates of  $t_{1/2}$  obtained by simultaneous scintigraphy:

**A. Ghos method**—(2) used all breath samples collected over a 4-hour time period. In this method the parameters  $a$ ,  $b$ , and  $c$  in the nonlinear model:

$$^{13}\text{CO}_2(t) = a \times t^b \times \exp(-c \times t)$$

are first estimated for each subject using a nonlinear least squares algorithm (PROC NLIN in the SAS ® package). The area under the predicted breath test concentration curve [i.e., the predicted values of  $^{13}\text{CO}_2(t)$  vs. time using the estimated parameter values for a, b, and c] for each subject was then computed via numerical integration (in the current study, the gamma function in SAS ® was used). Then these computed areas were “adjusted” by regressing the scintigraphic  $t_{1/2}$  values on these areas to obtain the following estimate of  $t_{1/2}$ :

$$(\text{adjusted}) t_{1/2} = -0.0494954 + 0.01277308 \times \text{area.}$$

**B. Total cumulative breath  $^{13}\text{CO}_2$  excretion**—(which used at least 12 breath samples collected over at least 4 hours). The rationale for including this additional analysis is based on the observation that the cumulative maximum  $^{13}\text{CO}_2$  excretion represents an objective parameter that is collected according to the test protocol and is not mathematically derived. The cumulative breath test values were then used to predict the scintigraphic  $t_{1/2}$  values using a simple exponential model (scintigraphic  $t_{1/2} = \eta \times \exp(-\theta \times \text{Cumulative BT value})$ ). The estimated coefficients in this model were,  $\eta = 290.4$ , and  $\theta = 0.0204$ .

**C. Wagner-Nelson method**—(13) used all breath samples collected over a 4-hour period. The Wagner-Nelson equation is:

$$F(t) = (A(\text{breath})(t) + C(t)/0.65) / A(\text{breath})(\infty),$$

where  $F(t)$  is a fractional dose of the  $^{13}\text{C}$  label emptied,

$C(t)$  is the  $^{13}\text{CO}_2$  excretion (% dose/h),

$A(\text{breath})(t)$  is the area under the  $C(t)$  curve (% dose) and

$A(\text{breath})(\infty)$  is the ultimate  $^{13}\text{CO}_2$  recovery in breath (% dose)

The fractional dose curve [ $F(t)$  vs.  $t$ ] for each subject is then treated as a “emptying curve” and  $t_{1/2}$  estimates obtained via, for example, linear interpolation.

**D. Generalized linear regression method [Viramontes (6)]**—used only 5 breath samples at 45, 90, 120, 150 and 180 minutes. In this method, the gastric emptying  $t_{1/2}$  is estimated directly as  $t_{1/2} = 1/LP_{1/2}$ , where  $LP_{1/2}$  (the “linear predictor”) is given by

$$LP_{1/2} = 0.0024 - 0.0038 \times ^{13}\text{C}_{45} + 0.0066 \times ^{13}\text{C}_{90} - 0.0042 \times ^{13}\text{C}_{120} + 0.0036 \times ^{13}\text{C}_{150} - 0.0012 \times ^{13}\text{C}_{180}$$

**E. Linear regression method [Szarka (7)]**—which used the same 5 breath samples at 45, 90, 120, 150 and 180 minutes. In this method, the  $^{13}\text{CO}_2$  values are used to compute estimates of the GE proportions at times  $t = 15$  to 240 minutes. The following formula summarizes the linear regression models and the coefficients are given in Table I.

$$\begin{aligned} \text{GE prop}_t = & \text{Intercept (t)} + B_{\text{Gender}}(t) * \text{Gender} + B_{\text{BMI}}(t) * \text{BMI} + B_{45}(t) * {}^{13}\text{CO}_2(\text{at 45 min}) \\ & + B_{90}(t) * {}^{13}\text{CO}_2(\text{at 90 min}) + B_{120}(t) * {}^{13}\text{CO}_2(\text{at 120 min}) \\ & + B_{150}(t) * {}^{13}\text{CO}_2(\text{at 150 min}) + B_{180}(t) * {}^{13}\text{CO}_2(\text{at 180 min}) \end{aligned}$$

For example, for  $t=30$  minutes, the estimated GE proportion is obtained by multiplying the values for gender (0=Females, 1=Males), BMI, and the  ${}^{13}\text{CO}_2$  values by their respective coefficients: 0.00980, -0.00655, -0.02590, -0.17187, 0.15184, -0.06426, and 0.03375 from Table I (30 min) and adding in the corresponding intercept term for 30 minutes to get an estimated GE proportion at 30 minutes. Doing this for each time point yields an estimated gastric emptying curve. The gastric emptying  $t_{1/2}$  values are then estimated via linear interpolation from the above computed GE proportions at the time points around  $\text{prop}_t=0.5$ .

### Statistical Analysis

The concordance correlation coefficient [CCC (14)] for the  $t_{1/2}$  results obtained with each method using breath test data were compared with the  $t_{1/2}$  results obtained with simultaneous scintigraphy. Scatter plots of the  $t_{1/2}$  values by scintigraphy (Y-axis) versus the various breath test method estimates of  $t_{1/2}$  (X axis) were made including the  $Y=X$  line to illustrate agreement for each method relative to the gold standard scintigraphic gastric emptying results. In addition, Bland-Altman plots are provided to compare the residuals to the average of the combination of methods for scintigraphy and each mathematical method using breath  $\text{CO}_2$  excretion.

## RESULTS

### Gastric Emptying

As previously published (6), the pharmacological modulation resulted in the expected prolongation of gastric emptying with atropine ( $207.9 \pm 72.6$  min [SD]), and acceleration with erythromycin ( $50.2 \pm 18.1$  min), both significantly different from control ( $100.7 \pm 20.2$  min).

Table II shows  $t_{1/2}$  results obtained by each method as well as the difference in estimated  $t_{1/2}$  relative to the gold standard scintigraphy. All methods, except for the Wagner-Nelson method, resulted in mean gastric emptying  $t_{1/2}$  values that approximated the data obtained with scintigraphy. Note however that, although the mean difference for several methods, is close to zero (other than the Wagner Nelson method, which shows several points falling far from the line of identity, as evident in Figure 1), there is a large standard deviation of the difference for the Ghoo's model and cumulative excretion methods. The smaller standard deviation typically indicates that there are fewer poorly fitted observations (the gold standard scintigraphy  $t_{1/2}$  values) with the linear regression (Szarka) and generalized linear regression (Viramontes) methods.

The scatter plots in Figure 1 illustrate the agreement for each mathematical model based on breath test values relative to the gold standard, scintigraphy. Points closer to the  $Y=X$  line indicate better agreement. Each data point in each plot represents the result for one individual participant, and the difference from the  $Y=X$  line reflects the discordance from the gold standard. The Bland-Altman plots in Figure 2 show the residuals or differences between the respective breath test and scintigraphic  $t_{1/2}$  data in relation to the average of the values by scintigraphy and the specific mathematical analysis. Note that the scatter of the residuals around the zero line (identity) is smallest for the Szarka and Viramontes methods.

### Correlation between Mathematical Analysis Methods

The highest concordance correlation coefficient was observed with the linear regression [Szarka] method (Table II). The simple cumulative excretion of breath  $^{13}\text{CO}_2$  method provided a better concordance correlation coefficient than the Ghooos method.

## DISCUSSION

In this technical evaluation of the mathematical models to estimate gastric emptying  $t_{1/2}$  relative to the simultaneous measurements using scintigraphy, the linear regression [Szarka] and generalized linear regression [Viramontes] methods appear to provide the best analyses of breath  $^{13}\text{CO}_2$  excretion in stable isotope gastric emptying breath tests. This study is the largest assessment of the different models in which the calculated gastric emptying parameters were observed with the same meal by simultaneous measurements with scintigraphy and breath test. Moreover, the database was selected to ensure that there was a broad spectrum of gastric emptying rates: accelerated normal or delayed. Therefore, the conclusions from our analysis are generalizable.

Whether the breath test is used for diagnostic purposes or to assess the effect of medication, it is critically important that the test is accurate. In this study, the different models have been applied to data obtained using the same meal, and the average  $t_{1/2}$  estimates are close to the scintigraphic data and therefore realistic. This contrasts with some data in the literature which provide unrealistic estimates of  $t$  lag and  $t_{1/2}$ , when using the Ghooos model method. For example, in a study using a dually radiolabeled muffin, the mean  $t$  lag measured by scintigraphy was  $42 \pm 19$  minutes, whereas the mean  $t$  lag obtained using the  $^{13}\text{C}$ -octanoic acid breath test (OBT) was  $121 \pm 25$  minutes and the overall mean  $t_{1/2}$  as measured by scintigraphy was  $104 \pm 24$  minutes (mean  $\pm$  SD) whereas, the mean  $t_{1/2}$  by OBT was  $212 \pm 52$  minutes (15).

The cumulative excretion model has the advantage that it uses the actual data collected during the study without the use of any weighting factors; it is therefore potentially more useful in laboratories that have not developed analysis by comparison with simultaneous scintigraphy. However, it does require collection of breath samples over 3–4 hours, and its correlation with scintigraphy does not reach the level observed with the Szarka and Viramontes models which require a small number of breath samples, and are therefore more cost-effective. Thus, one advantage of the linear regression [Szarka] and generalized linear regression [Viramontes] methods is that they require a smaller number of breath samples, typically 5, to obtain the estimates of gastric emptying; this also reduces the cost of the test since it reduces the number of breath samples requiring collection, containers, mailing to a central laboratory and analysis. The linear regression [Szarka] models is also versatile and can be converted to estimate the proportion remaining in the stomach at defined times (e.g. at 1, 2 and 4 hours after meal ingestion).

We conclude that, since the linear regression [Szarka] and generalized linear regression [Viramontes] methods require relatively few (e.g. 5) breath samples and the analysis provides the closest agreement with  $t_{1/2}$  results based on scintigraphy, these methods provide the best analyses of breath  $^{13}\text{CO}_2$  excretion in stable isotope gastric emptying breath tests. The data (coefficients) provided in table I provide the reader with the opportunity to use the linear regression [Szarka] method to estimate a gastric emptying curve from measured breath  $^{13}\text{CO}_2$  excretion. From these estimated GE proportions, an estimated  $t_{1/2}$  value could be obtained. Measurement of the percent retention at specified time points is of interest, and it may reflect gastric emptying rates more accurately than gastric emptying  $t_{1/2}$  if the latter analysis is limited to a few scans at defined times, such as 1, 2 and 4 hours. However, it is worth noting that, in this study, gastric emptying was measured by means of scans obtained every 15 minutes for the first 2 hours and every 30 minutes for the next 3 hours (total 5 hours). Moreover, other

relevant summaries of a gastric emptying curve (e.g., a gastric emptying lag time, proportion remaining at 3-hours) can easily be calculated from the estimated GE proportions with the information available. Finally, studies in patients with gastroparesis (rather than pharmacologically-induced gastric emptying delay) would be of interest to confirm the conclusions on the optimal pharmacological models used with the breath test. This has been performed with the Szarka model (7) which included approximately 43% of patients with delayed gastric emptying.

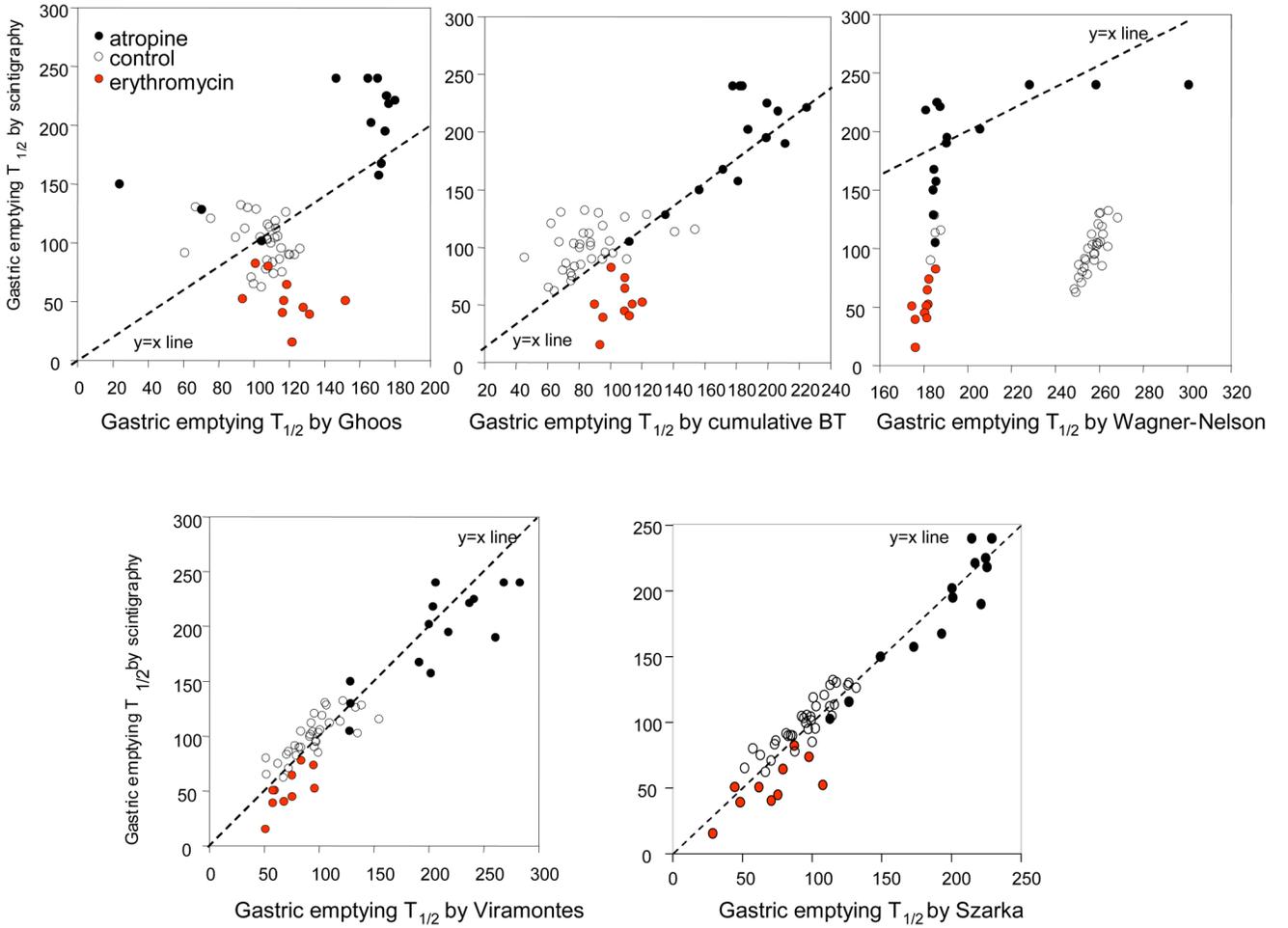
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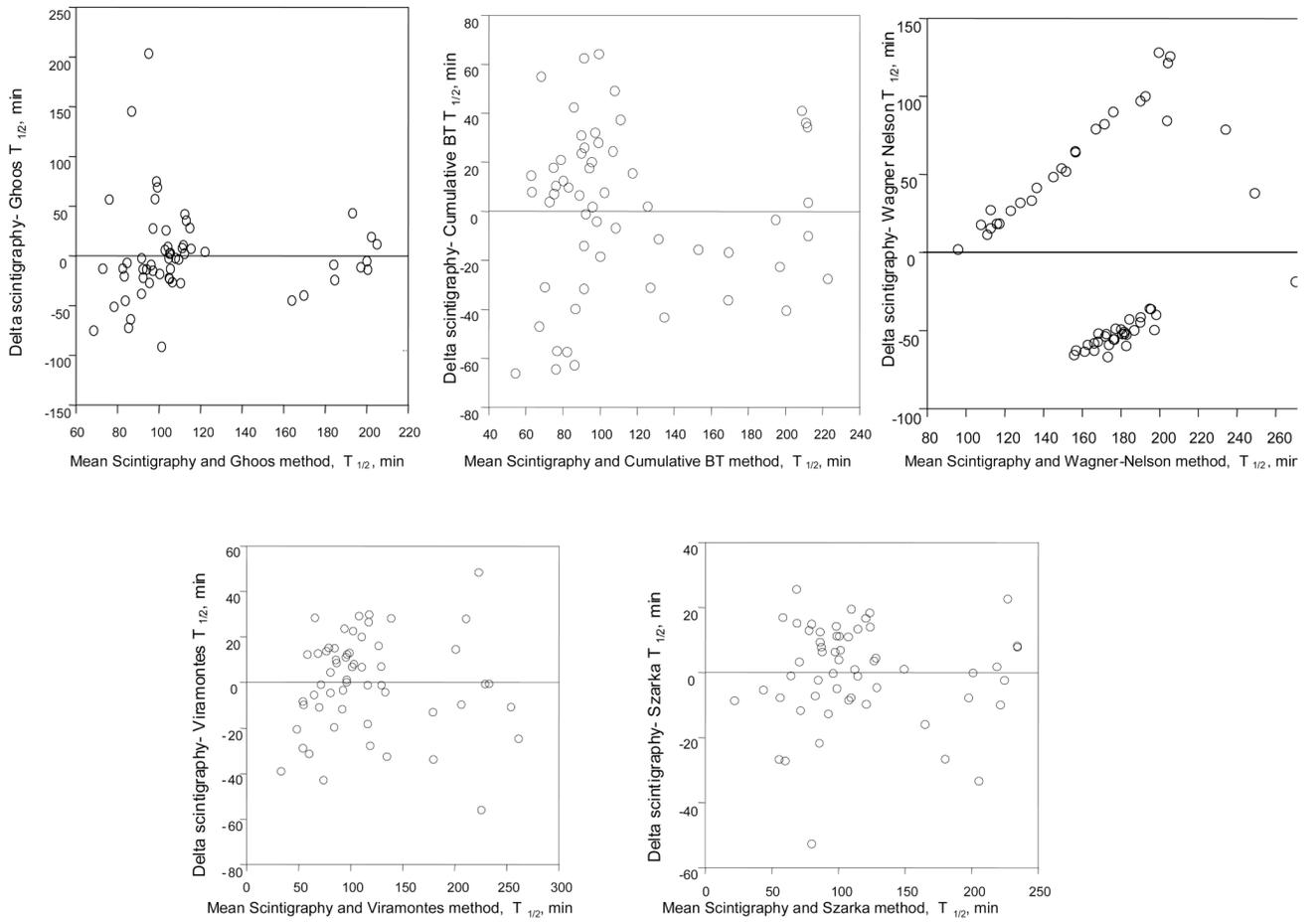
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**Figure 1.** Scatter plots for each mathematical model used for breath test relative to scintigraphic gastric emptying  $t_{1/2}$  measured simultaneously. Data are separated for the participants receiving atropine, erythromycin and controls. Note i.v. atropine retarded and i.v. erythromycin accelerated gastric emptying relative to controls as shown by the data corresponding to the Y axis. Note also that the data with breath test analyzed by Viramontes and Szarka models most closely approximate the  $y=x$  line and are clustered according to gastric emptying category.



**Figure 2.** Bland Altman for each mathematical model used for breath test relative to scintigraphic gastric emptying  $t_{1/2}$  measured simultaneously.

**Linear Regression Model (Szarka method) Coefficients for Estimating Gastric Emptying Proportions Obtained via Scintigraphy Using Individual Breath <sup>13</sup>CO<sub>2</sub> Excretion Data**

Table 1

| GE prop <sub>t</sub><br>at t=(min) | Intercept | Gender   | BMI      | B <sub>45</sub> (t) | B <sub>90</sub> (t) | B <sub>120</sub> (t) | B <sub>150</sub> (t) | B <sub>180</sub> (t) |
|------------------------------------|-----------|----------|----------|---------------------|---------------------|----------------------|----------------------|----------------------|
| 15                                 | 1.09476   | -0.01908 | -0.00415 | -0.00320            | -0.11959            | 0.11568              | -0.02513             | -0.00296             |
| 30                                 | 1.12249   | 0.00980  | -0.00655 | -0.02590            | -0.17187            | 0.15184              | -0.06426             | 0.03375              |
| 45                                 | 1.11271   | 0.01303  | -0.00687 | 0.01437             | -0.22596            | 0.16223              | -0.08794             | 0.05765              |
| 60                                 | 1.04898   | 0.02113  | -0.00538 | 0.05942             | -0.25427            | 0.14985              | -0.10530             | 0.07821              |
| 75                                 | 1.07397   | 0.02773  | -0.00537 | 0.15000             | -0.30612            | 0.15117              | -0.12109             | 0.07300              |
| 90                                 | 1.06163   | 0.02812  | -0.00467 | 0.17145             | -0.29358            | 0.13126              | -0.14364             | 0.07598              |
| 105                                | 1.09566   | 0.01673  | -0.00611 | 0.19115             | -0.21736            | 0.03825              | -0.12854             | 0.06893              |
| 120                                | 1.09889   | 0.00833  | -0.00595 | 0.17042             | -0.17673            | 0.03345              | -0.15714             | 0.06451              |
| 150                                | 1.05673   | -0.00527 | -0.00596 | 0.15955             | -0.10749            | 0.03581              | -0.18595             | 0.03408              |
| 180                                | 1.07560   | 0.00231  | -0.00886 | 0.10135             | -0.03675            | 0.00027              | -0.13224             | -0.02133             |
| 210                                | 0.90088   | 0.00457  | -0.00698 | 0.06637             | -0.02634            | 0.02323              | -0.12215             | -0.03186             |
| 240                                | 0.71615   | -0.00362 | -0.00487 | 0.06655             | -0.02279            | 0.00428              | -0.08159             | -0.03467             |

**Table II**  
**Comparison of  $t_{1/2}$  Results by Scintigraphy and Mathematical Models Using Breath Test Data**  
 $t_{1/2}$  results (Mean  $\pm$  SD, min and [range]) obtained by each method and difference in estimated  $t_{1/2}$  (mean  $\pm$  SD and [range]) relative to the gold standard, scintigraphy

| Method                            | Scinti-<br>graphy                     | Ghoos                     | Cum. <sup>13</sup> CO <sub>2</sub><br>excretion | Wagner<br>-Nelson          | Viramontes               | Szarka                   |
|-----------------------------------|---------------------------------------|---------------------------|---|----------------------------|--------------------------|--------------------------|
| $T_{1/2}$                         | 114 $\pm$ 55 (16 to 240) <sup>†</sup> | 117 $\pm$ 31 (24 to 179)  | 113 $\pm$ 46 (45 to 225)                        | 225 $\pm$ 38 (175 to 301)  | 118 $\pm$ 60 (51 to 282) | 115 $\pm$ 53 (29 to 229) |
| $\Delta t_{1/2}$ vs. scintigraphy | -----                                 | -4 $\pm$ 47 (-106 to 126) | 1 $\pm$ 35 (-78 to 62)                          | -112 $\pm$ 65 (-187 to 39) | -4 $\pm$ 22 (-71 to 34)  | -1 $\pm$ 15 (-55 to 26)  |
| CCC                               | -----                                 | 0.43                      | 0.77  | 0.01                       | 0.93                     | 0.96                     |

<sup>†</sup>Three subjects had censored  $t_{1/2}$  values (i.e.,  $t_{1/2}$  > 240 minutes)  
 Cum=cumulative;  $\Delta$ =delta; CCC= concordance correlation coefficient