Review

Stable isotope breath tests for assessing gastric emptying:
A comprehensive review

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Abstract

A stable isotope (13C) breath test is a promising method for assessing gastric emptying, but it has not been pervasive yet in Japan. We think that there are some barriers to its popularization, including the uncertainty concerning its theoretical backgrounds, the ambiguity of analyzing and interpreting the data, and the lack of standard protocols for breath sampling. The aim of the present review is to break through these barriers. We hope this article could make the 13C-gastric breath test more maneuverable for and more accessible to researchers and clinicians.

Key words: breath test, gastric emptying, the JSSMR standard protocol, loss, retention

Introduction

An array of techniques are currently available for assessing gastric emptying, including scintigraphy, ultrasonography, magnetic resonance imaging, acetaminophen absorption, and breath testing with a stable isotope (13C) (Schmidt et al., 2008; Parkman et al., 2009). Of these techniques, the 13C-breath test fulfills all the demand and desires for non-invasive investigations: it is free from radiation hazards, requires neither a skillful hand of the expert nor multiple venipuncture for blood sampling, and can be performed easily and repeatedly (Schmidt et al., 2008; Parkman et al., 2009). The accuracy of the breath test is well supported by a series of validation studies reporting a strong correlation between the breath test and the scintigraphy, which is the “gold standard” for measuring gastric emptying (Ghoos et al., 1993; Braden et al., 1995; Delbende et al., 2000; Chey et al., 2001; Bromer et al., 2002; Chew et al., 2003; Braden et al., 2004). Regardless of its promising nature, however, the breath test is not so prevalent as might has been expected in Japan. We conjecture that there are some barriers to its popularization. The likely barriers that render one hesitant to use it are as follows. First, albeit the methodological principle of breath testing is apparently reasonable, it does not convincingly explain the reason why a real...
pattern of gastric emptying is not in agreement with a corresponding pattern of breath output (Sanaka et al., 2005a; Sanaka et al., 2008; Bluck et al., 2009). The unconvincing explanation leaves behind some doubt on the credibility of the breath test. Second, the way of summarizing and interpreting breath-test results is ambiguous (Schommartz et al., 1998; Bluck, 2009). The ambiguity has led to a longstanding debate. Last of all, since a myriad of protocols have been proposed, breath-test users are bothered in determining which to select (Nakada et al., 2002). Development of a standard protocol is warranted.

The aim of the present review is to overhaul the [13C]-gastric breath test; special concern is placed on breaking through the above-mentioned barriers. We hope this article could make the [13C]-gastric breath test more maneuverable for and more accessible to researchers and clinicians.

**Theoretical backgrounds of the [13C]-gastric breath test**

*Conventional model for explaining the breath test theory*

A conventional scenario on which the [13C]-gastric breath test theoretically relies is as follows (Ghoos et al., 1993; Perri et al., 1998) (Fig. 1). After consumption of a test meal marked with [13C]-acetate for liquids or [13C]-octanoate for solids, the [13C]-substance remains intact in the stomach and is rapidly absorbed upon the passage of the pyloric ring. Subsequently, the labeled compound undergoes prompt and complete hepatic oxidation to [13CO2], which is released into the venous blood and then is breathed out eventually. The sequence of events occurring between the stomach and the lung is assumed to be “a one-way direct road” (Fig. 1), suggesting that the pulmonary excretion of [13CO2] corresponds to gastric emptying of [13C]-acetate/octanoate in a one-to-one manner. However, the one-to-one manner is incompatible with the fact that the breath output response is apart from the emptying input (Lee et al., 2000; Sanaka et al., 2008; Bluck, 2009). The truth is that the customary scenario is misleading albeit simple: the simplicity is attained only at the expense of overshadowing the more complex aspects of kinetics of the [13C] label (Sanaka et al., 2008).
Revised model for explaining the breath test theory

To give firm credence to the breath test, a more decent model for explaining its theory is presented, in which how the human body handles the $^{13}$C label is meticulously illustrated (Fig. 2) (Sanaka et al., 2008). The following points in the explanatory model should be stressed. First, although the intestinal absorption is considered to be immediate, the labeled octanoate in the chyme may take a longer time to be absorbed in the small intestine than the labeled acetate in the liquid phase (Sanaka et al., 2007a). However, the magnitude of the time-difference would be minimal. Second, the liver extracts a portion of the $^{13}$C label from its total dose absorbed by incorporating the $^{13}$C label into non-$^{13}$CO$_2$ metabolites (e.g., ketone bodies). This hepatic disposal of the label (metabolic loss) is substantial: about 50% of the $^{13}$C label goes missing, thereby never being exhaled as available breath data (Sanaka et al., 2008). Third, since the diffusion of carbon dioxide through the alveolar membrane is physiologically regulated, only a limited fraction of the $^{13}$CO$_2$ entering the pulmonary circulation is expired. In this sense, the lung actually serves as “a two-way forked road” that allocates the $^{13}$CO$_2$ either to the expired air or to the systemic circulation. Fourth, part of the $^{13}$CO$_2$ in the systemic circulation is eliminated via the non-pulmonary route (e.g., feces and urine). The non-pulmonary loss is, however, so tiny as to be negligible (Sanaka et al., 2008). Lastly, the $^{13}$CO$_2$ circulating around the body penetrates various organs (e.g., heart and skeletal muscle) and stays there for a substantial period before being expelled. The organs (the bicarbonate pool) functionally work to reserve the $^{13}$CO$_2$ and, consequently, delaying its recovery (retention) (van Nieuwenhoven et al., 1999; Sanaka et al., 2008).

We should pay heed to the loss and the retention, which are the bottom line for accounting for...
the discrepancy between gastric emptying of the $^{13}$C label and the pulmonary recovery of $^{13}$CO$_2$ (Sanaka et al., 2008; Bluck, 2009). Independently of gastric emptying, the retention delays the pulmonary $^{13}$CO$_2$ output and the loss makes the recovery of the output incomplete (Fig. 3). Nonetheless, the pulmonary $^{13}$CO$_2$ output is considered to reflect gastric emptying, because the loss and the retention are much less variable between and within individuals than gastric emptying (Sanaka et al., 2008). This fact ensures the methodological relevance of the $^{13}$C-acetate/octanoate breath test.

**Analysis and interpretation of breath test results**

**Analysis of breath data**

Breath $^{13}$CO$_2$ data are usually expressed in percentage terms: the percent dose $^{13}$C-recovery per hour (PDR; % dose/h) and the cumulative percent dose $^{13}$C-recovery during a certain period (CPDR; % dose). The PDR (% dose/h) values are converted into the CPDR (% dose) values by means of the trapezoidal rule or mathematical integration; in reverse, the former are obtained by mathematical differentiation of the latter. The PDR and CPDR values are plotted against time (PDR[t] and CPDR[t] curve) for data analysis. Note that the breath output is modified by the loss and the retention, independently of gastric emptying (Sanaka et al., 2008; Bluck, 2009) (Fig. 3).

A multitude of breath-test parameters have been proposed (Ghoos et al., 1993; Braden et al., 1995; Schommartz et al., 1998; Kulik et al., 2001; Sanaka et al., 2004; Sanaka et al., 2005; Bluck et al., 2006; Sanaka et al., 2006; Sanaka et al., 2007a). Of these, the half-emptying time ($T_{1/2b}$), the lag phase ($T_{lag}$), and the gastric emptying coefficient (GEC) have been quoted frequently, all of which were first reported in the Ghoos’s epoch-making paper (Ghoos et al., 1993). By original definition,
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T_{1/2b} indicates the time by which half of the total cumulative recovery of the $^{[13]C}$ label (CPDR[$\infty$]/2) is attained, and T_{lag} designates the time at which the $^{[13]CO_2}$ excretion rate (PDR[t]) reaches its maximal level. GEC does not have a meaningful definition, only being described as “an overall index of gastric emptying” (Ghoos et al., 1993). According to the Ghoos’s analytical procedure, GEC, T_{lag} and T_{1/2b} are computed by fitting the CPDR[t] and the PDR[t] plots onto the following power exponential model:

$$\text{CPDR}[t] = m(1 - e^{-kt})^\beta.$$  \hspace{1cm} \text{Eq. 1}

Since the PRR[t] function is expressed as the first derivative of the CPDR[t] function, it is given by:

$$\text{PDR}[t] = mk\text{e}^{-kt}(1 - e^{-kt})^{\beta - 1}.$$  \hspace{1cm} \text{Eq. 2}

Alternatively, the PDR[t] function can be modeled on the $\chi^2$-distribution in statics as:

$$\text{PDR}[t] = a t^b \text{e}^{-ct}.$$  \hspace{1cm} \text{Eq. 3}

In all the equations, t is time in hours, and m, k, $\beta$, a, b, and c are all constants; the constant of m is an estimate of the ultimately cumulative recovery (CPDR[$\infty$]). These model functions are empirically deduced from the global appearance of actual $^{[13]CO_2}$ data plot without any physiological relevance (Bluck et al., 2006). It should be acknowledged that the constants of a and m determine the vertical scale (“height”) of the PDR [t] and the CPDR [t] curves, while the other constants determines the appearance (“shape”) of the curves (Bluck et al., 2006). By the computerized curve-fitting algorithms, all the constants are extracted, and then the outcome parameters are calculated as:

$$\text{GEC} = \ln (a) \text{ (from Eq. 3)},$$  \hspace{1cm} \text{Eq. 4}

$$\text{T}_{\text{lag}} (h) = \frac{\ln(\beta)}{k} \text{ (from Eq. 1 or 2)} \text{ or } \frac{b}{c} \text{ (from Eq. 3)}, \text{ Eq. 5}$$

$$\text{T}_{1/2b} (h) = \frac{-1}{k}\ln(1 - 2^{-1/\beta}) \text{ (from Eq. 1 or 2)}. \hspace{1cm} \text{Eq. 6}$$

In case a computer is not at hand, T_{lag} can be determined directly by visual inspection of the “raw” PDR-data plot (Braden et al., 1995).

**Interpretation of breath-test parameters**

The physiological meaning of the three parameters has rarely been scrutinized (Sanaka et al., 2008). Given the discrepancy between breath-test results and real emptying processes, it is hard to specify what process of gastric emptying corresponds to each of the three popular parameters. For instance, as discussed below, what T_{lag} exactly signifies is a state of flux. The lag phase originally means the time for the stomach to grind and mix ingested food before gastric emptying starts. In scintigraphic measurements, the lag phase is arbitrarily defined as the initial post-meal period during which only a small portion of food (5\%-10\%) leaves the stomach (Mariani et al., 2004). In breath testing, on the other hand, more than 80\% of the gastric content leaves the stomach by the time at which the $^{[13]CO_2}$ excretion rate is maximized, namely T_{lag} (Nakada et al., 2002). In this sense, a view that T_{lag} corresponds to the lag phase is unreasonable (Kitagawa et al., 2002; Zai et al., 2002). At present, we think it more pragmatic to consider that what the
parameters indicate is merely whether gastric emptying is rapid, normal, or slow.

In pharmacokinetic models, the absorption of drugs is described by two different terms, the extent and the rate of absorption (Basson et al., 1996). Following this way of thinking, it is quite operative to view the $[^{13}\text{C}]$CO$_2$ recovery from the two separate standpoints, the amount and the velocity of the recovery: the amount is represented by the area under the PDR[t] curve until the infinite time, namely CPDR[$\infty$], and the velocity is represented by the shape of the PDR[t] and CPDR[t] curves (Table 1). A general rule for the amount-velocity concept is that: 1) as gastric emptying of the $[^{13}\text{C}]$ label is enhanced (suppressed), the amount of $[^{13}\text{C}]$CO$_2$ recovery is increased (decreased) and the velocity of $[^{13}\text{C}]$CO$_2$ recovery is hastened (slowed) (Fig. 4), and 2) without any change in gastric emptying, the loss and the retention modify the amount and the velocity, respectively, thereby “contaminating” the breath output data (Table 1).

Needless to say, the rate of gastric emptying is the velocity, and therefore, the velocity-related parameter is more suitable for the breath test than the amount-related one. $T_{lag}$ and $T_{1/2b}$ reflect the velocity but are unrelated to the amount of the label recovery (Ghoos et al., 1993; Sanaka et al., 2008). The interpretation of the two parameters is plain: a shorter (longer) $T_{lag}$ or $T_{1/2b}$ indicates faster (slow) gastric emptying. In contrast to $T_{lag}$ and $T_{1/2b}$, which are intuitively understandable, what GEC represents is somewhat vague. GEC is a direct function of the constant of $a$ (Eq. 4), implying that it is more closely associated with the amount than with the velocity (Table 1) (Sanaka et al., 2008). From the implication of the amount, a larger (smaller) GEC is considered to indicate faster (slower) gastric emptying. Even though a high correlation was documented between GEC and the half-emptying time measured by the scintigraphy ($T_{1/2s}$) (Ghoos et al., 1993), GEC would theoretically be unsuitable as an emptying index because of its amount-related nature. Recently, GEC seems out of vogue (Shishido et al., 2002).

As mentioned above, the loss and the retention have the delusive influence on the breath-test results, namely on GEC, $T_{max}$, and $T_{1/2s}$; the loss and the retention are the confounding factor for the gastric breath test. The susceptibility of the three parameters to the loss and the retention should be taken into account in interpreting the breath-test results (Fig. 5). A few research groups have devised more sophisticated strategies that can weed out the loss and retention factors from breath data (Sanaka et al., 2004; Bluck et al., 2006). However, the novel analytical strategies have not been widely endorsed yet.

### Table 1. Mutual relationships among key concepts

<table>
<thead>
<tr>
<th>Breath $[^{13}\text{C}]$CO$_2$ Recovery</th>
<th>Time-recovery curve</th>
<th>Constant in the model functions*</th>
<th>Confounding factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount</td>
<td>Area under the PDR[t]</td>
<td>$a$ value</td>
<td>Loss</td>
</tr>
<tr>
<td>CPDR[$\infty$]</td>
<td>$m$ value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity</td>
<td>Shape of the curve</td>
<td>$b$ and $c$ values</td>
<td>Retention</td>
</tr>
<tr>
<td></td>
<td>$k$ and $\beta$ values</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PDR[t]: percent dose recovery (% dose/h); CPDR[t]: cumulative percent dose recovery (% dose). *PDR[t] = \(a t^b e^{-c t}\) and CPDR[t] = \(m (1 - e^{-k t})^\beta\).
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Debate on breath-test parameters

Since the introduction of the $^{13}$C-octanoic acid breath test by Ghoos et al. in 1993, some issues on the breath-test parameters have been disputed. Weighing these debates is essential for a better understanding of the breath test.

Several authors uphold an opinion that the terms of “the half-emptying time” ($T_{1/2b}$) and “the lag phase” ($T_{lag}$) are used equivocally (Schommartz et al., 1998; Nakada et al., 2002). The two terms were originally applied to characterize a real pattern of gastric emptying, which is “directly” assessed by the intubation technique or the scintigraphy. Application of the two terms to the “indirect” breath test necessarily incurs confusion. The improper application would be attributed to use of the power exponential functions for curve-fitting analysis in the scintigraphy ($\text{Gastric retention} = 1 - (1 - e^{-kt})^{\beta}$) (Siegel et al., 1988) and in the breath test ($\text{CPDR}[t] = m(1 - e^{-kt})^{\beta}$): the two functions are inherently the same; therefore, whichever equation is used, the half-

Fig. 4. Changes in breath-test results in response to those in the amount and the velocity of the $^{13}$CO$_2$ recovery. PDR$[t]$ is the percent dose recovery (% dose/h), and CPDR $[t]$ is the cumulative recovery (% dose). The premise is that as gastric emptying of the $^{13}$C label is enhanced (suppressed), the amount of $^{13}$CO$_2$ recovery is increased (decreased) and the velocity of $^{13}$CO$_2$ recovery is hastened (slowed). As the amount is increased (decreased), the PDR$[t]$ and the CPDR$[t]$ curves are heightened (lowered) without an essential change in the shape of the curves (A and B); a faster (slower) gastric emptying is indicated by the larger (smaller) vertical scale of the curves. As the velocity is accelerated (decelerated), the PDR $[t]$ curve is steepened (flattened) without a change in its area under the curve (C) and the CPDR $[t]$ curve is moved rightward (leftward) without a change in the ultimate cumulative recovery (CPDR $[\infty]$) (D); a faster (slower) gastric emptying is indicated by the steepened (flattened) shape of the curves.
emptying time is expressed as \((-1/k)\ln(1 - 2^{-1/β})\ln(β)/k\) and the lag phase as \((-1/k)\ln(1 - 2^{-1/β})\).

Again, it should be noted that the pulmonary \([^{13}\text{C}]\) recovery curve is different from the scintigraphic emptying curve by nature. Some workers think it more appropriate to name \(T_{1/2b}\) “the half-\([^{13}\text{CO}_2]\) recovery (or excretion) time” (Kulik et al., 2001; Zai et al., 2009). Likewise, not a few authors feel that “the lag” in \(T_{lag}\) is a bit of misnomer (Clegg et al., 2010) and the abbreviation of \(T_{max}\) is suitable for the time to the maximal \([^{13}\text{CO}_2]\) excretion instead of \(T_{lag}\) (Takahashi et al., 2006; Sanaka et al., 2007b; Sanaka et al., 2008; Iwase et al., 2009; Shindo et al., 2009; Mishima et al., 2009). In this context, \(T_{lag}\) is replaced by \(T_{max}\) afterward in the present review.

Our revised explanatory model suggests that the difference between \(T_{1/2b}\) and \(T_{1/2s}\) is attributed to the time for the delay in pulmonary \([^{13}\text{CO}_2]\) recovery due to the retention (Sanaka et al., 2008) (Figs. 2 and 3). Formerly, the regression equation of \(T_{1/2s}\) (min) = \(T_{1/2b}\) (min) – 66 was preferably used to adjust \(T_{1/2b}\) to \(T_{1/2s}\), assuming that the difference of 66 min is constant between individuals (Ghoos et al., 1993). However, the rationale for adjusting \(T_{1/2b}\) has been challenged, because the
difference is more variable than constant (Choi et al., 1997; Lee et al., 2000), the way of deriving the equation is not adequate (Lee et al., 2000; Sanaka et al., 2003), and the adjustment procedure rarely yields additional diagnostic information (Schommartz et al., 1998).

It is reasonable to consider that a high statistical correlation between $T_{\text{max}}$ and $T_{1/2b}$ reported (Schommartz et al., 1998; van Nieuwenhoven et al., 1999; Shishido et al., 2002) justifies the mutual exchange of the two parameters, either of which could be rejected according to researchers’ preferences. Generally, $T_{1/2b}$ seems more popular than $T_{\text{max}}$, despite a lack of tangible supportive evidence (Sanaka et al., 2007b). Some investigators, however, are skeptical about the primacy of $T_{1/2b}$: rather, they are confident that $T_{1/2b}$ is inferior to $T_{\text{max}}$ as an emptying measure based on the following observations. First, $T_{1/2b}$ is less sensitive than $T_{\text{max}}$ in detecting an early postprandial change in gastric emptying (Sanaka et al., 2007b). This finding is quite understandable, considering that the CPDR[t] curve changes minimally while the PDR[t] curve does dynamically in the early phase (Zai et al., 2009). Next, $T_{1/2b}$ would be prone to mistakenly judge a “normal” emptying to be “delayed” in case that the PDR[t] curve exhibits a very gentle descending slope (Shirasaka et al., 2002; Shishido et al., 2002; Lee et al., 2000; Sanaka et al., 2007b); in such a case, we speculate that the retention, rather than a real delay in the emptying, makes the pulmonary $[^{13}\text{CO}_2]$ recovery drag on long after the emptying terminates. On the other hand, $T_{\text{max}}$ has a disadvantage that its precise determination is difficult when sampling frequency is spares or the PDR[t] curve is so flattened in shape that its peak is unclear.

Protocol for the $[^{13}\text{C}]$-breath test

Sampling frequency and duration

To date, a pile of studies have been conducted with breath testing under variable protocols. The difference in sampling frequency and test duration between the protocols are a matter of great concern (Clegg et al., 2010), because the sampling schedule largely affects the precision and the feasibility of the breath test. A strict protocol with too many sampling points over a protracted period increases the precision, whereas it spoils the feasibility.

Under the curve-fitting approach, the reliability of the breath-test parameters highly depends on how well a plot of actual $[^{13}\text{CO}_2]$ data fits each of the model functions. In general, the shorter the test duration, the poorer the curve fit; this phenomenon is more manifest as gastric emptying is more delayed. In the $[^{13}\text{C}]$-octanoate breath test, $T_{1/2b}$ and $T_{\text{max}}$ (Tlag) values are more variable and more erratic as a sampling period is shorter (Choi et al., 1997; Delbende et al., 2000; Lee et al., 2000; Gonlachanvit et al., 2001). Concerning the duration, some authors believe that a 4-h study is sufficient to keep its reliability (Ghoos et al., 1993; Bromer et al., 2002; Yamamoto et al., 2004), while others have claimed that a shorter timeline of $\leq 6$ h is suboptimal (Choi et al., 1997; Clegg et al., 2010). Regarding the frequency, a number of investigators deem that sampling at 15-min intervals is appropriate (Maes et al., 1998; Clegg et al., 2010). In order to guarantee the precision of curve-fitting analysis, a criterion has been advocated that any breath test with poor curve-fit (the $r^2$ coefficient $< 0.9$) should be rejected (Perri et al., 1998). Under this strict criterion, however, the feasibility of the test would dwindle considerably, especially in case of the delayed emptying. On the other hand, in the $[^{13}\text{C}]$-acetate breath test, few studies have investigated the optimal test
duration. After all, a scheme for sample collection is still more optional, but we consider that the most practical and prevalent schedule at present is a 4-h timeframe with breath samples being collected at 15-min intervals for solid-meal studies (Perri et al., 2010) and more frequently (e.g., at 5-min intervals during the early postprandial phase) for liquid-meal studies (Nakada et al., 2002). If subjects are highly suspicious of having delayed gastric emptying or higher-caloric meals are used for the test, a 6-h timeframe would be preferable.

We have a suspicion about the validity of the model-dependent analytical strategy, which forces biological variability in the breath output pattern (namely, gastric emptying) to be fitted into a “ready-made” non-biological mold. In real, there exist pathological patterns of gastric emptying that are not fitted to the available model functions (Zai et al., 2009). In this context, the model-independent T max, which is determined visually, would play a more important role. The accuracy of Tmax would be equivalent either based on the curve-fitting or based on the visual inspection, if only breath samples are collected frequently (Braden et al., 1995; Nakada et al., 2002). In addition, the test duration could effectively be shortened using the visually determined Tmax because most of the descending phase of the plot is unnecessary for the determination (Nakada et al., 2002; Shishido et al., 2002). There seems no particular reason for use of the model-dependent Tmax over the more convenient, model-independent one.

Standardized protocol for breath testing

In the face of confusion about the sampling scheme, the standardization of the breath test protocol has been necessitated. To the best of our knowledge, two standardize protocols for breath testing have been reported; one has been proposed by the Japan Society of Smooth Muscle Research (JSSMR) for the [13C]-acetate breath test (Nakada et al., 2002) and the other by the Italian Group for Gastric Emptying Testing (IGGET) for the [13C]-octanoate breath test (Perri et al., 2010). These standard protocols are expected to settle the problem originating from non-uniformity of protocols across institutes.

Table 2. Protocol for the [13C]-acetate breath test standardized by the Japan Society of Smooth Muscle Research (The JSSMR protocol)

| Test meal: a commercialized liquid meal (200 kcal/200 mL) (e.g., RACOL®, Otsuka, Tokyo) |
| [13C]-compound: 100 mg [13C]-sodium acetate |
| Sampling frequency and duration: at time 0 (preprandial baseline), 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210, and 240 min |
| Parameter: T1/2b, Tmax-calc, Tmax |
| Reference range: T1/2b (59.8 – 122.6 min), Tmax-calc (32.8 – 74.4 min), Tmax (23.3 – 64.5 min) |

Note
1) The reference ranges are derived from 63 healthy volunteers (19 – 51 years, 34 males and 29 females). The mean (SD) values are 91.2 (15.7) min for T1/2b, 53.6 (10.4) min for Tmax-calc, and 43.9 (10.3) min for Tmax.
2) Tmax-calc is calculated by the Ghoos’s curve-fitting technique, and Tmax is determined by directly inspecting the [13CO2] % dose/h curve.
3) Liquid test meals from different manufacturers are applicable to this protocol if the meals contain 200 kcal/200 mL.

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The JSSMR protocol is made as a consensus guideline for the [13C]-acetate breath test (Table 2). In 2001, the working party, which comprises JSSMR expert members, was convened from nine different institutions to discuss how to develop a standardized protocol for breath testing, setting the primary goal of making the breath test more accessible not only to researchers but also to clinicians. Over the one-year thorough discussion, the JSSMR protocol was yielded and was then promulgated at the JSSMR 44th annual meeting (Sendai, Miyagi, July 2002). The hallmark of the JSSMR protocol is its simplicity: the test meal is a ready-made liquid, which is sanitary and easy to prepare; in busy clinical settings, the foreshoetened 90-min version is also available, by which clinicians can discriminate between normal and abnormal gastric emptying based on the visually determined T_max and its reference values (23.3–64.5 min).

Recently, clinical and experimental studies using the JSSMR protocol have increasingly been published (Takahashi et al., 2006; Iwase et al., 2009; Shindo et al., 2009; Mishima et al., 2009). The working party also dedicated to standardizing the protocol for the [13C]-octanoate breath test. Regrettably, however, this attempt ended up coming at a standstill, because the consensus regarding a standard solid meal could not be reached.

More recently, the IGGET protocol has been elaborated for the [13C]-octanoate breath test (Table 3). The attempt to standardize a solid test meal has resulted in admirable success by adopting a manufactured muffin meal, which can be prepared with minimally complicated procedures. The reference range for T_{1/2b} has been determined from a large database, therefore being highly reliable.

The two standard protocols would make the breath test more viable and maneuverable. However, both protocols are still conditional, and further augments are crucial in search of more optimal ones.

### Table 3. Protocol for the [13C]-octanoate breath test standardized by the Italian Group for Gastric Emptying (The IGGET protocol)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test meal</td>
<td>a manufactured muffin containing 378 kcal (EXPIROGer®, Sofar, SpA Milan)</td>
</tr>
<tr>
<td>[13C]-compound:</td>
<td>100 mg [13C]-octanoic acid</td>
</tr>
<tr>
<td>Sampling frequency and duration:</td>
<td>at time 0 (preprandial baseline) and at 15-min intervals for 240 min</td>
</tr>
<tr>
<td>Parameter:</td>
<td>T_{1/2b}</td>
</tr>
<tr>
<td>Reference range:</td>
<td>T_{1/2b} (upper limit; 146 min)</td>
</tr>
</tbody>
</table>

**Note**
1) The reference ranges are derived from 131 healthy volunteers (47 ± 18 years, 58 males and 73 females). The mean (SD) value is 89 (29) min.
2) T_{1/2b} is calculated by the Ghoos’s curve-fitting technique.
3) Age and gender do not influence the reference value.

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The two standard protocols would make the breath test more viable and maneuverable. However, both protocols are still conditional, and further augments are crucial in search of more optimal ones.

### Conclusion

The [13C]-breath test is a promising method, although some problems remain unsolved. We expect that more clinicians and researchers use it in their practical and experimental work.
References


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