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CLINICAL RESEARCH

Short- and medium-term reproducibility of gastric emptying of a solid meal determined by a low dose of ^{13}C-octanoic acid and nondispersive isotope-selective infrared spectrometry

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Abstract

AIM: To evaluate the reproducibility of a modified ^{13}C breath test-based measurement of solid phase gastric emptying (GE) within the frames of a simple-repeated measure study protocol.

METHODS: Twelve healthy subjects (6 females and 6 males, mean age 24.9 ± 0.7 years) were recruited to undergo three identical GE examinations. In six subjects the first two examinations were performed 2 d apart, and the third session was carried out at a median interval of 19.5 d (range 18 - 20 d) from the second one. In another six subjects the first two measurements were taken 20 d apart (median, range: 17-23 d), whereas the third session took place 2 d after the second one. Probes of expiratory air collected before and during six hours after intake of a solid meal (378 kcal) labelled with 75 μL (68 mg) ^{13}C-octanoic acid, were measured for $^{13}CO_2$ enrichment with the nondispersive isotope-selective infrared spectrometry NDIRS apparatus.

RESULTS: Taking coefficients of variation for paired examinations into account, the short-term reproducibility of the GE measurement was slightly but not significantly better than the medium-term one: 7.7% and 11.2% for the lag phase (T-Lag), 7.3% and 10.9% for the gastric half emptying time (T½). The least differences in GE parameters detectable at $P = 0.05$ level in the 12 paired examinations were 9.6 and 15.6 min for T-Lag, 11.6 and 19.7 min for T½ by a two-day or two to three-week time gap, respectively.

CONCLUSION: The low-cost modification of the breath test involving a lower dose of ^{13}C-octanoic acid and NDIRS, renders good short- and medium-term reproducibility, as well as sensitivity of the measurement of gastric emptying of solids.

Key words: ^{13}C breath test; Gastric emptying; Nondispersive isotope-selective infrared spectrometry; ^{13}C-octanoic acid; Reproducibility

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INTRODUCTION

Since its first description and validation in 1993[1], ^{13}C-octanoic acid breath test (^{13}C-OABT) has dug its way towards the top of the list of the most widely used methods for the measurement of gastric emptying of solids. For example, recently published epidemiologically-oriented studies addressing the features of gastric emptying kinetics in large cohorts of patients involving hundreds of subjects suffering from functional dyspepsia, have been performed with ^{13}C-OABT[2-4]. Also the introduction of less expensive and technically demanding apparatus, based on the nondispersive isotope-selective infrared spectrometry (NDIRS), is an undeniable milestone which has opened the gate for a widespread use of ^{13}C breath tests[5-7], the ^{13}C-OABT making no exception in this respect[8-13].

Reproducibility is a vital feature of any measurement or diagnostic method used in medical practice. Few data are available on the repeatability of the ^{13}C-OABT in humans, and reports addressing this subject appear unsatisfactory[14,18]. Moreover, no previous study has reported reproducibility of the NDIRS variety of the ^{13}C-OABT. The aim of this study was to establish the short- and medium-term repro-

ducibility of the ^{13}C-OABT with NDIRS and a reduced dose of the ^{13}C substrate.

MATERIALS AND METHODS

Subjects

Twelve healthy subjects (6 females and 6 males) were recruited to participate in this study, their mean age was 24.9 ± 0.7 years, and the average body mass index amounted to 22.37 ± 1.06 kg/m^2.

During a screening interview, the participants declared themselves to be in full health according to the World Health Organisation criteria. Exclusion criteria comprised a history of surgery affecting the digestive tract anatomy with the exception of appendectomy, current use of any drugs which might affect gastrointestinal motility, and pregnancy. The recruitment procedure involved performance of a standard breath test with ^{13}C-urea, so that exclusively subjects with a negative test result for *Helicobacter pylori* infection were admitted. Except for three persons, all the participants were non-smokers. The study was conducted in accordance with the Helsinki Declaration, and each volunteer gave a written consent after getting information as to the aim, protocol and methodology of the study. During the introductory interview, the subjects were committed not to eat any food of naturally increased ^{13}C content, such as products made of maize, cane sugar, pineapple, kiwi fruit for 48 h preceding the examination.

Experimental protocol

Each subject underwent three sessions of gastric emptying measurement held on separate days. In six subjects the first two examinations were performed 2 d apart, and the third session was carried out at a median interval of 19.5 d (range 18-20 d) from the second one. In another six subjects, the first two gastric emptying measurements were taken 20 d apart (median, range 17-23 d), whereas the third session took place 2 d after the second one. The assignment of the order of intervals separating the sessions (short-long or long-short) was randomized. Ultimately the short-term reproducibility assessment involved performance of 12 pairs of gastric emptying examinations separated by a two-day break, whereas twelve pairs of examinations accomplished at a median interval of 21.5 d (range 17-23 d) were dedicated for the evaluation of the medium-term reproducibility.

The research was performed on volunteers who reported themselves to the laboratory in the morning, after a 12-h overnight fasting and abstaining from cigarette smoking (if applicable). At the beginning, a basal fasted probe of the exhaled air was put into an aluminium-covered plastic bag of about 1 L capacity (Fisher Analysen Instrumente GmbH, Germany). At the time point of "0", the subjects were given a solid test meal, a pancake made of two eggs, 30 g wheat flour and 0.1 g baking powder, which was additionally smeared with 50 g of strawberry jam before serving. The total energy content of the meal was 1574 kJ (378 kcal) and it contained 15.5 g proteins, 16.8 g fat, and 43.0 g carbohydrates. During the preparation procedure of the pancake, the two-egg yolks were temporarily separated from the egg whites and thoroughly mixed with 75 μL (68 mg) of ^{13}C-octanoic acid (INC610P, lot #T012A-L3241, Euriso-Top, France) which was instilled with a precision digital micropipette (Calibra 822-20/200, Socorex, Switzerland). Thereafter the yolks were added to and stirred with the remaining ingredients with an electric mixer. Finally the dough was transferred into a pan and fried to firm consistency with addition of 5 mL of sunflower oil. The time needed to consume the test meal did not exceed 10 min. No drink was served with the meal because the study intended to assess strictly the reproducibility of the solid phase gastric emptying.

Reckoning the passage of time from the defined "0" point, 26 probes of the expiratory air were collected postprandially every 10 min during the first hour, and then every 15 min for an additional 5 h. After ingestion of the meal, the subjects were asked not to take any additional food or drink for 6 h. They were enabled to rest sitting in a comfortably furnished room and allowed to watch video films.

Measurement of $^{13}CO_2$ and derivation of gastric emptying parameters

Concentrations of $^{13}CO_2$ in the probes of the exhaled air were measured with the NDIRS apparatus (*IRIS*, Wagner Analysen Technik Vertriebs GmbH, Germany; a model equipped with 16 ports for simultaneous mounting of bags with air samples was used). Repeatability of the $^{13}CO_2$ measurement with the NDIRS technique was checked by double measurements performed on 96 probes of the exhaled air originating from 3 randomly selected gastric emptying examinations. The procedure was performed in such a way that the second measurement was taken instantly without removing the bags containing the probes from the apparatus.

The determined $^{13}CO_2$ content within the total pool of the exhaled CO_2 was expressed in δ‰ PDB units, i.e. relative to the international standard - the calcium carbonate of the fossil Belemnitella of the cretaceous Pee Dee formation in South Carolina, USA (zero δ‰ PDB corresponds to 1.12372% ^{13}C atoms within $CaCO_3$). The obtained δ‰ PDB data were exported to an ASCII file for a subsequent analysis with a user-created Excel spreadsheet.

The changes in $^{13}CO_2$ concentration were recalculated to net increments expressed in ‰ DOB (*delta over baseline*) units according to the formula:

$$DOB_i = \delta‰\ PDB_i - \delta‰\ PDB_0$$

where **i** stands for the probe number, and the 0 index pertains to the basal probe of the expiratory air.

The momentary ^{13}C recovery at time i, D%$_i$_^{13}C, expressed in percent age of administered dose per hour (% dose per hour), was computed according to the equation:

$$D\%_i\_^{13}C = 100 \cdot (DOB_i/1000 \cdot 0.0112372 \cdot TCO_2) / dose$$

where TCO_2 = total expiratory CO_2 production in mmol/h and dose = amount in mmol of ^{13}C-octanoic acid given to the subjects. The TCO_2 was derived by multiplication by the rate of 300 mmol/m^2 per hour by the body surface area computed according to the formula by Haycock *et al*[19].

The ^{13}C recovery within a given period, C$_i$_^{13}C, ex-

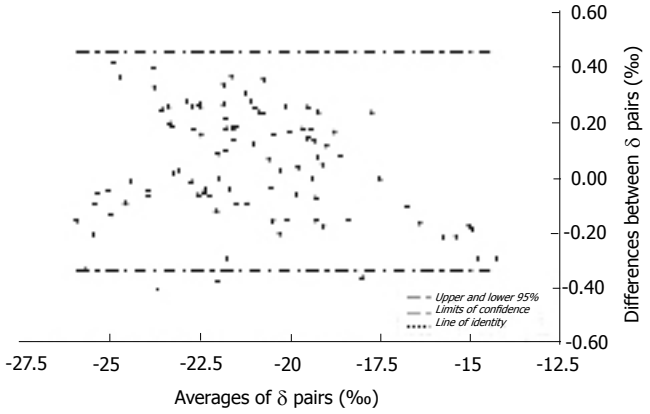

Figure 1 Repeatability of the measurement of $^{13}CO_2$ enrichment (δ) in expiratory air after intake of a solid meal labeled with 75 μL (68 mg) ^{13}C-octanoic acid. Ninety-six pairs of δ measurements taken from three randomly selected examinations were considered.

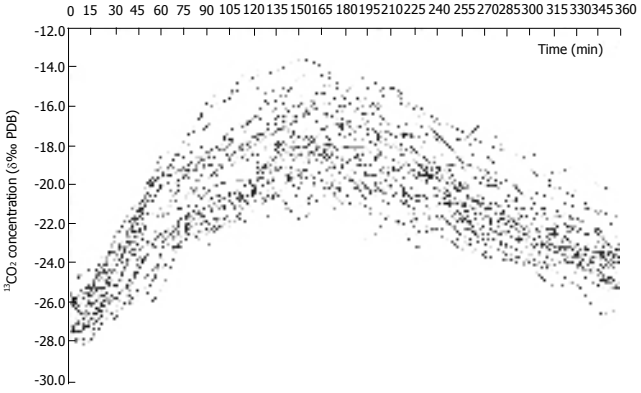

Figure 2 Individual curves reflecting the increment in $^{13}CO_2$ enrichment in exhaled air after intake of a 378 kcal solid meal containing 75 μL (68 mg) ^{13}C-octanoic acid (the 36 curves were obtained in 12 healthy subjects at three separate days).

pressed in percent age of dose, was computed following the trapezoid rule:

$C_i\_^{13}C = 0.5 \cdot (DOB_{i-1} + DOB_i)/1000 \cdot \triangle t \cdot 0.0112372 \cdot TCO_2 / dose$

where $\triangle t$ = the time span between consecutive DOB measurements

The cumulative ^{13}C recovery T_i -^{13}C in percent age of administered dose was then derived from a stepwise summation of $C_i\_^{13}C$ for i within the domain of 1 - 26.

Using algorithms of non-linear regression implemented in the Statistica 6.1 software[20], the curves of momentary ^{13}C recovery were fitted to the function:

$D\%_i\_^{13}C = at^be^{-ct}$

where t stands for time, and a, b, c are parameters of the function

which enables computation of three gastric emptying parameters[1, 21]: the lag phase, T-Lag = b/c; the gastric half emptying time, T½ = Gamma inv. (0.5; b+1; 1/c); and the gastric emptying coefficient, GEC = ln(a)

Statistical analysis

A null hypothesis, assuming a zero difference between repeated measurements, was checked with the paired Student's *t* test. The reproducibility of the gastric emptying parameters was expressed in terms of the coefficient of variation for paired examinations, CV_p[22,23]. Moreover Bland and Altman statistics was applied in order to calculate the repeatability coefficient, RC[24,25]. Finally, $\triangle_{0.05}$ - the least statistically significant difference detectable at P=0.05 level (two-tailed) was calculated for each gastric emptying parameter[26]. Results were presented as mean ± SE. All statistical analyses were performed with the Statistica 6.1 software, licence # adbp409a903816ar[20].

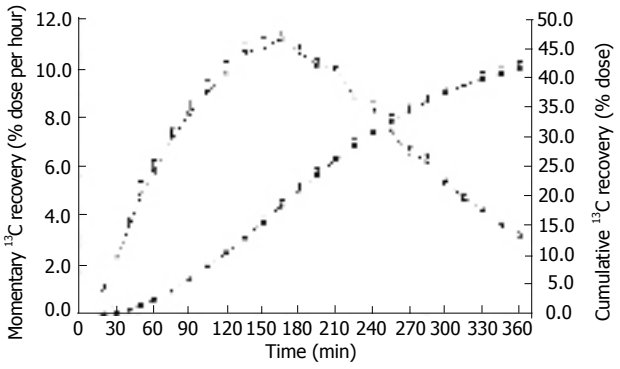

Figure 3 Momentary (empty squares) and cumulative (filled squares) ^{13}C recovery in exhaled air after ingestion of a 378 kcal solid meal containing 75 μL (68 mg) ^{13}C-octanoic acid. The data are grand means with standard errors (bars) calculated on average values obtained in 12 healthy volunteers during three examinations carried out on separate days.

RESULTS

Repeatability of NDIRS measurement of $^{13}CO_2$ enrichment in exhaled air

Bland and Altman statistics performed on the paired measurements of the $^{13}CO_2$ content within 96 samples of the expiratory air yielded a repeatability coefficient of 0.40‰, and the mean difference between the repeated measurements amounted to 0.07‰ (95% confidence interval: 0.34 - 0.46‰) (Figure 1). If the data pertaining to the $^{13}CO_2$ content within the expiratory air were expressed in terms of the delta over baseline values, the respective repeatability coefficient amounted to 0.62‰, with a mean difference of 0.28‰ between repeated measurements (95% confidence interval: 0.34 - 0.90‰).

Reproducibility of parameters characterizing gastric emptying kinetics

Ingestion of the solid test meal labeled with 75 μL of ^{13}C-octanoic acid brought about an expected increase of the $^{13}CO_2$ concentration in the exhaled air (Figure 2). The maximum net increment in the $^{13}CO_2$ concentration amounted to 9.1‰ (mean, 95% confidence intervals 5.3‰ to 12.9‰) during the 36 gastric emptying examinations. The maximum momentary ^{13}C recovery in the exhaled air was observed at 165 min (mean, 95% confidence intervals 112 min to 219 min) postprandially, and amounted on average to 11.50 ± 0.36 % dose per hour (Figure 3). During the whole 6 h observation period 41.80 ± 1.13 % of the administered tracer was eliminated in the form of $^{13}CO_2$ within the expiratory air (Figure 3).

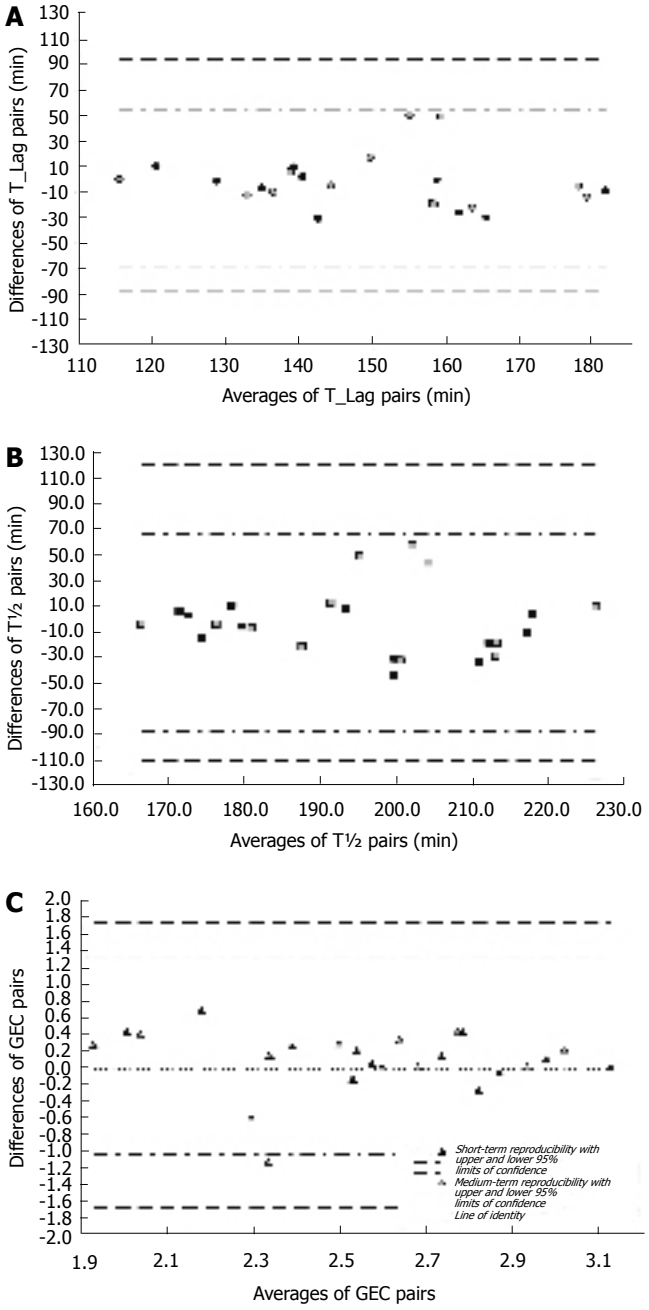

Figure 4 Bland and Altman statistics (plot of differences between pairs *vs* their names) of the short-(open symbols) and medium-term(filled symbols) reproducibility of the measurement of the lag phase (T-Lag, panel A), the gastric half emptying time (T½ , panel B), and the gastric emptying coefficient (GEC, panel C) of the solid phase gastric emptying with a breath test using 75 μL (68 mg) ^{13}C-octanoic acid and the isotope-selective nondispersive infrared spectrometry. On each panel the respective borders of the 95% confidence intervals are plotted - cf. the legend of the GEC graph, panel C.

A graphical depiction of the Bland and Altman statistics pertaining to the gastric emptying parameters is given in Figure 4, and a comprehensive statistical description of the reproducibility data is provided in Table 1. In no instance the null hypothesis of a zero difference between the repeated measurements had to be discarded. According to the data assembled in Table I, greater values of RC and CV_p characterized the medium-term compared to the short-term reproducibility. A comparison of the absolute values of the differences between the paired measurements implied rejection of a hypothesis that reproducibility of the gastric emptying was significantly worse when the examinations were separated by an extended time gap.

DISCUSSION

The novelty of the results furnished by the current study consists in: for the first time the reproducibility of the ^{13}C-OABT was evaluated with the NDIRS, a reduced dose of the ^{13}C-octanoic acid was applied for the test, the test meal was administered without allowance of any intake of liquids so that pure repeatability of the solid phase gastric emptying could be discerned, and a distinguishment was made between the short- and medium-term reproducibility.

Typically the ^{13}C-OABT is performed with 100 μL of ^{13}C-octanoic acid which is equivalent to 91 mg[2-5,8-12,14,16-18]. It was reported that a lower dose - 50 mg ^{13}C-octanoic acid can be used to examine the solid phase gastric emptying[21]. The NDIRS apparatus coped well with the 68 mg (75 μL) amount of ^{13}C-octanoic acid applied for labelling the test meal in the current study. This contention is supported by the finding of a low value of the repeatability coefficient (0.40‰) and a narrow 95% confidence interval of the differences between paired measurements of $^{13}CO_2$ enrichment (0.34 - 0.46‰) derived from a large number of breath samples covering a typical range of $^{13}CO_2$ concentration encountered throughout the 6 h of the ^{13}C-OABT. Since baseline fluctuation of $^{13}CO_2$ concentration in breath is expected to approach a standard deviation of 0.72‰[27], our results clearly indicate that the measurement error involved in the NDIRS technique is less than the natural baseline fluctuation of $^{13}CO_2$ concentration in breath. The finding quoted is in concordance with our previously published results[6,7,28].

While performing the ^{13}C-OABT, we generously allowed for a frequent sampling of the expiratory air (a total of 27 samples were collected throughout a single examination including the basal specimen) over a long observation period of 6 h. This approach was substantiated by findings of other authors clearly stating that too short a collection period and/or an infrequent sampling of the expiratory air may lead to erroneous estimation of the parameters of gastric emptying with the ^{13}C-OABT[16,17,29]. According to Choi *et al*[16,17], duration of the ^{13}C-OABT obligatory should be extended to six hours, since largely overestimated values of T_Lag and T½ would be derived from the data truncated to four hours.

Three parameters are originally proposed as quantitative descriptors of the gastric emptying kinetics examined with the ^{13}C-OABT, namely: T_Lag, T½, and GEC[1,21]. Nowadays researchers are increasingly inclined to use the T ½ only when reporting on their results with the ^{13}C-OABT. This apparently minimalistic approach has quite firm grounds. The shortcomings of GEC consist in the fact that its estimation is not independent of the endogenous CO_2 production, and in the case of fast gastric evacuation patterns this parameter may underestimate gastric emptying[1]. T_Lag of the ^{13}C-OABT is originally conceived to reflect the duration of the first phase of gastric evacuation, while the solid meal is ground to particles of 1-2 mm in diameter before the actual emptying can start. This assumption has not found any convincing corroboration in vali-

Table 1 Reproducibility of solid gastric emptying measurement with breath test at a 68 mg (75 μL) dose of ^{13}C-Octanoic acid and isotope-selective nondispersive infrared spectrometry

Observed values[1]	T-Lag, lag phase 149.7 ± 4.6 min		T½, gastric half emptying time 195.6 ± 4.2 min		GEC, gastric emptying coefficient 2.56 ± 0.09	
	Short-term	Medium-term	Short-term	Medium-term	Short-term	Medium-term
RC (min)	31.6	46.7	39.1	59.1	0.61	0.87
CVp (%)	7.7	11.2	7.3	10.9	8.3	12.5
△ 0.05 (min)	9.6	15.6	11.6	19.7	0.17	0.29

Short-term reproducibility involved twelve paired examinations performed 2 d apart, whereas medium-term reproducibility involved twelve paired examinations at a median interval of 21.5 d (range 17 - 23 d)

RC = repeatability coefficient, CVp = coefficient of variation for paired examinations, △ 0.05 = the least statistically significant difference detectable at $P = 0.05$ level, two-tailed

[1] These data are grand means calculated on average values obtained during three examinations carried out on separate days

dation studies of the ^{13}C-OABT against the scintigraphic determination of gastric emptying, which is the so called '*golden standard*' in the field of gastro-emptology[16,17]. Quite recently it was even demonstrated by Doppler ultrasonography that transpyloric flow starts already during ingestion of a ^{13}C-labelled solid meal, which results in a detectable excretion of $^{13}CO_2$[30]. It has been shown that trituration of the solid meal can lead to a pronounced shortening of this parameter[31]. Nevertheless, T_Lag will be more and more willingly replaced by the term '*time to reach the maximum of the momentary $^{13}CO_2$ excretion*' which is the revised representation of what the T-Lag derived mathematically from the function fitted to a $^{13}CO_2$ excretion curve actually is[1,8,9,21].

In the present study, we controlled rigorously and kept constant a number of factors which might affect reproducibility of the ^{13}C-OABT, namely meal composition, time of the day when the gastric emptying measurement was taken, posture of the subjects during the test. Ingestion of the test meal took place irrespective of actual phase of the duodenal migrating motor complex (MMC), because monitoring of the duodenal motor activity would require insertion of a manometric tube into the lumen of the duodenum - an invasive manoeuvre which might interfere with physiological conditions assumed for the ^{13}C-OABT performance; observation of a particular phase of the duodenal MMC could not ameliorate the reproducibility of the scintigraphic measurement of the gastric empting of the solid phase of a meal[32]. Homogeneity was the important feature of the test meal we applied, that is the pancake was uniformly labelled with ^{13}C-octanoic acid and eaten without addition of any liquid to assure the sole assessment of the reproducibility of the solid phase gastric emptying [33].

Because there are no other reports on the ^{13}C-OABT performed with the NDIRS, our data can be compared only to the results obtained by other authors applying the isotope ratio mass spectrometry (IRMS). Choi *et al*[17] reported that the reproducibility of T-Lag and T½ is 14% and 15% respectively. In the study by Delbende *et al*[18] the pertinent RC and CV_p amounted to 35.5 min and 14.3%, respectively. The reproducibility results of those two studies look very much alike indeed. The results of the present study indicated that the reproducibility of gastric emptying of solids determined by ^{13}C-OABT and the NDIRS was not worse than that by IRMS. Moreover, both the reproducibility and sensitivity (as assessed by the magnitude of the least detectable differences in the gastric emptying parameters) were preserved when the examinations were separated by a two- three-week time gap. Finally, it should be emphasized that the results obtained by others[17,18] and coming from our current study clearly demonstrate that the reproducibility of the measurement of gastric emptying of solids by the ^{13}C-OABT is equivalent to the intra-subject variability of the solid-phase gastric emptying observed with gamma scintigraphy[22,23]. This is an important finding due to the inherently indirect nature of ^{13}C-OABT. The reproducibility of ^{13}C-OABT would be affected by more factors than a scintigraphic GE measurement, namely the intestinal absorption of the ^{13}C-octanoic acid, its oxidation to $^{13}CO_2$ within the liver, as well as kinetics of the subsequent transfer of $^{13}CO_2$ to the expiratory air.

In conclusion, the low-cost modification of the breath test involving a lower dose of ^{13}C-octanoic acid and NDIRS, renders a good short- and medium-term reproducibility, as well as sensitivity of the measurement of gastric emptying of a solid meal.

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