Correlation of electrogastrography and gastric emptying rate estimated by ^{13}C-octanoic acid breath test in healthy volunteers

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Summary

Gastric emptying is one of the most important motor functions of the gastrointestinal tract. Direct measurement of gastric emptying is considered to be a crucial diagnostic test for gastrointestinal motor dysfunction. The aim of this prospective project was to assess possible correlation of electrogastrography and ^{13}C-octanoic acid breath test as a measure of gastric emptying in healthy adult volunteers (5 men and 5 women, aged 20-48 years, mean 32; 50 % of subjects were Helicobacter pylori positive). There was a significant negative correlation between half-life of elimination in ^{13}C-octanoic acid breath test (using a solid test meal) and percent activity of normal rhythm in postprandial electrogastrography recording (r = -0.632; p = 0.0498). Helicobacter pylori negative subjects had a higher percent activity of a normal rhythm and faster gastric emptying of solids compared to Helicobacter pylori positive persons, this difference was not statistically significant. In conclusion, electrogastrography and gastric emptying rate, assessed by ^{13}C-octanoic acid breath test, are suitable non-invasive complementary methods to investigate the motor function of the stomach. The major parameters of electrogastrography and half-life of elimination (in ^{13}C-octanoic acid breath test) mutually correlate in healthy subjects.

KEY WORDS: *GASTRIC EMPTYING, ^{13}C-OCTANOIC ACID BREATH TEST, ELECTROGASTROGRAPHY, HEALTHY VOLUNTEERS*

Souhrn

Korelace elektrogastrografie a rychlosti žaludeční evakuace stanovené dechovým testem s kyselinou ^{13}C-oktanovou u zdravých dobrovolníků

Evakuace žaludku je jednou z nejdůležitějších motorických funkcí gastrointestinálního traktu. Přímé měření žaludečního vyprazdňování má zásadní význam pro diagnostiku dysmotilitních poruch trávicího ústrojí. Cílem této prospektivní studie byla korelace elektrogastrografie a dechového testu s kyselinou ^{13}C-oktanovou jako ukazatele žaludeční evakuace u zdravých dospělých dobrovolníků (5 mužů, 5 žen, ve věku 20–48 let, průměr 32; 50 % osob bylo Helicobacter pylori pozitivních). Byla zjištěna statisticky významná negativní korelace poločasu eliminace (dechového testu s kyselinou ^{13}C-oktanovou při použití pevného testačního pokrmu) s procentuálním zastoupením normálního rytmu při postprandiálním záznamu elektrogastrografie (r = -0,632; p = 0,0498). U Helicobacter pylori negativních osob bylo vyšší procentuální zastoupení normálního rytmu a rychlejší žaludeční vyprazdňování pevné potravy ve srovnání s Helicobacter pylori pozitivními osobami, tento rozdíl však nebyl statisticky významný. Elektrogastrografie a rychlost žaludeční evakuace, stanovená dechovým testem s kyselinou ^{13}C-oktanovou, jsou vhodné neinvazivní, navzájem se doplňující metody k vyšetření motorické funkce žaludku. Hlavní ukazatele elektrogastrografie a poločas eliminace dechového testu s kyselinou ^{13}C-oktanovou spolu u zdravých osob navzájem korelují.

KLÍČOVÁ SLOVA: *EVAKUACE ŽALUDKU, DECHOVÝ TEST S KYSELINOU ^{13}C-OKTANOVOU, ELEKTROGASTROGRAFIE, ZDRAVÍ DOBROVOLNÍCI*

INTRODUCTION

Gastric emptying is one of the most important motor functions of the gastrointestinal tract. Direct measurement of gastric emptying is considered to be a crucial diagnostic test for gastrointestinal motor dysfunction. Scintigraphy has been assumed to be a "gold standard" for gastric emptying evaluation to date [7,53]. However, it needs expensive equipment and induces a significant radiation burden [46].

Octanoic acid, an eight-carbon medium-chain fatty acid, is not absorbed from the stomach. However, once it reaches the duodenal lumen, octanoic acid is rapidly absorbed through intestinal mucosa and oxidised to CO_2 in the liver. Ghoos et al [20] proposed a radioactive carbon-labelled octanoic acid breath test for non-invasive measurement of gastric emptying rate of solids. Subsequently radioactive carbon ^{14}C has been replaced by ^{13}C. Carbon ^{13}C is a non-radioactive, natural and stable isotope and thus its use has been widely recommended both for research and clinical practice [56]. Several breath tests with stable isotopes have been developed to reliably assess gastric emptying of both solids and liquids [46]. Breath tests using ^{13}C-labelled test meals are based on the principle that the gastric emptying of the tracer substance proceeds simultaneously with the emptying of the labelled phase of the test meal. After delivery from the stomach the tracer is rapidly absorbed and oxidised to labelled carbon dioxide which is rapidly exhaled [3,19]. Because gastric emptying is the rate-limiting step for the absorption of medium-chain fatty acids, the fraction of ^{13}C expired in the breath (as $^{13}CO_2$) indicates the rate of gastric emptying [58]. In spite of several different protocols published, the ^{13}C-octanoic acid breath test has not been standardized yet. We developed our own method of the ^{13}C-octanoic acid breath test [6], expresing results of the breath test as a half-life of elimination. The half-life of elimination ($t^1/_2E$) of the administered carbon ^{13}C (in minutes) is a linear function of half-time of gastric emptying, duodenal absorption, transport and intermediate metabolism of ^{13}C-octanoic acid [6,13]. According to different studies, the intermediate metabolism of ^{13}C-octanoic acid represents 66 min [20] or 76.5 ± 7.5 min in adult subjects [6].

Surface electrogastrography (EGG) is a non-invasive method for clinical assessment of gastric myoelectrical activity. Neuromuscular activities of the stomach generate electrical phenomena termed “gastric slow waves”. They originate in a “pacemaker region” located on the greater curvature of the stomach near the junction of the fundus and proximal gastric corpus. The normal gastric slow-wave frequency is 3 cycles per minute (a 3-cpm rhythm) [8,9,11,12,18,27].

Simultaneous investigation of both EGG and ^{13}C-octanoic acid breath test may be useful to evaluate the efficiency of gastric emptying and underlying myoelectrical activity [49]. However, the relationship of EGG and gastric emptying rate remains controversial [2,39,50]. The aim of this prospective project was to assess possible correlation of EGG and ^{13}C-octanoic acid breath test as a measure of gastric emptying in healthy adult volunteers.

METHODS

Healthy volunteers

Ten healthy volunteers entered the study, 5 men and 5 women (aged 20-48 years, mean 32). 50 % of subjects were Helicobacter pylori positive. All persons underwent all EGG and 2 ^{13}C-octanoic acid breath tests (one with a solid meal and another one with a semi-solid test meal) within two weeks.

Electrogastrography

Surface cutaneous EGG was recorded using a Digitrapper EGG (Synectics Medical AB, Stockholm, Sweden) in the morning both fasting (30 min) and after meals (30 min). The standard solid test meal was used containing scrambled egg (+ 3 g of sunflower oil), white bread (40 g), butter (10 g) and still water (200 mL), with a total energy value of 1,178 kJ [29]. Patients were lying in a supine position during the EGG recording. Running spectral analysis (based on Fourier transform) was used for the evaluation of the EGG. Results were expressed as running spectrum percent activity. Spectral peaks were classified into 4 rhythm categories: bradygastria (EGG wave pattern < 2.4 cycles per minute - cpm), normal slow-wave rhythm (2.4–3.6 cpm; normal three-cycle per minute rhythm), tachygastria (3.6–9.9 cpm) and duodenal rhythm (10–15 cpm) [27].

The ^{13}C-octanoic acid breath test

The ^{13}C-octanoic acid breath test was performed using 100 mg ^{13}C-sodium octanoate (Cambridge Isotope Laboratories, Andover, USA) for each test. The solid test meal was of the same content and energy as that for EGG. The semi-solid meal (1,020 kJ) contained milk pudding (200 g) and still water (200 mL). Duplicate breath samples were obtained before (time zero) and every 15 min after eating the test meal during the following 255 min. Altogether 720 breath samples were analysed twice by means of isotope ratio mass spectrometry (AP 2003, Analytical Precision, Northwich, United Kingdom). Mass spectrometry results were expressed as the difference of $^{13}CO_2/^{12}CO_2$ ratios in the measured sample of exhaled breath and reference gas (SIAD Szendioxid, MSZ 209 15; CO_2 99.995 %). Helium was used as a carrier (SIAD 6.0; He > 99.9995 %). The baseline value at time was zero (δ_0) and particular values at relevant time t (δ_t) were used for calculation of both tests in all subjects [6]. To assess the half-life of elimination ($t^1/_2E$), we modelled the process of elimination with the incomplete gamma-function, which has a convenient form for the empiric plotting of breath test data [42].

Helicobacter pylori status

Helicobacter pylori status was investigated by means of ^{13}C-urea breath test. Citric acid solution (3 g dissolved in 150 mL of still water) was used as a test drink [30]. All subjects ingested

100 mg ^{13}C-urea (Helicobacter Test Hp Plus, Utandningstester i Sverige AB, Göteborg, Sweden) dissolved in 50 mL of still water with 1 g citric acid. Baseline and test breath samples were collected in duplicate at time 0 and after 30 min. Breath samples were analyzed twice by means of isotope ratio mass spectrometry (AP 2003, Analytical Precision, Northwich, United Kingdom). Cut-off was 3.5 (grey zone range 3.3–3.7). No borderline or discrepant results were found.

Statistical analysis

Data were statistically treated by means of descriptive statistics, paired t-test and Spearman rank order correlation using the SigmaStat software (Jandel Corp., Erkrath, Germany).

RESULTS

The overall results of ^{13}C-octanoic acid breath test and EGG are given in Tabs 1 and 2. The half-life of elimination using a solid test meal was significantly longer compared to a semi-solid test meal ($p < 0.001$). Running spectrum percent activity of EGG was not significantly different in fasting and postprandial recording and they did not correlate mutually. There was a significant negative correlation between half-life of elimination in ^{13}C-octanoic acid breath test (using a solid test meal) and a 3-cpm percent activity in postprandial EGG recording ($r = -0.632$; $p = 0.0498$). There was no correlation between running spectrum percent activity and half-life of elimination when a semi-solid test meal was used, see Figure for details. There were no significantly different results between men and women. Helicobacter pylori negative subjects had a higher percent activity of a 3-cpm rhythm and faster gastric emptying of solids compared to Helicobacter pylori positive persons (Tab. 3). However, this difference was not statistically significant.

DISCUSSION

The aim of our study was to estimate possible correlation of EGG and ^{13}C-octanoic acid breath test as a measure of gastric emptying in healthy adult volunteers. EGG is a non-invasive means of recording human gastric myoelectrical activity or slow waves from cutaneous leads placed over the stomach. In healthy volunteers, EGG exhibits sinusoidal waveforms with a predominant frequency of 3 cycles per minute. Some patients with nausea, vomiting, or other dyspeptic symptoms exhibit EGG rhythm disturbances or blunting of meal-evoked EGG signal amplitude increases. These abnormalities correlate to some degree with delayed gastric emptying of solids. In selected patients, EGG may be complementary to gastric emptying testing [44,60].

The gastric emptying of solid, semi-solid and liquid meals differs greatly. Storing of solids (predominantly in the fundus) causes a characteristic lag phase before the emptying as a suspension of small particles starts in an approximately linear fashion. The gastric emptying of liquids follows a non-linear exponential pattern and it is more affected by volume and gravity [3]. Gastric slow waves control the frequency and propagation of the gastric contractions. Since the dominant EGG frequency reflects the frequency of the gastric slow waves, this dominant frequency is associated with gastric motility and determines the maximum frequency of gastric contractions [10,16,26].

In our study, normal 3-cpm rhythm (2.4–3.6 cpm) for > 60 % of recording time during fasting was found in 7/10 (for > 70 %: 6/10) healthy subjects. In the first postprandial 30 min, normal 3-cpm rhythm (2.4–3.6 cpm) for > 60 % of recording time was found in 6/10 (for > 70 %: 4/10) healthy volunteers. The lower limit (mean minus 2 SD) of percentage time of normal 3-cpm rhythm in our setting was 60 % (in fasting) and 55 % (in postprandial period), respectively. According to the American Motility Society [44], normal EGG frequency (2.0–4.0 cpm) should

Table 1 Electrogastrography in ten healthy adult subjects. Results are given as running spectrum percent activity (mean ± standard deviation).

Recording	3-cpm	Bradygastria	Tachygastria	Duodenal activity
Fasting	72.8 ± 16.9	8.4 ± 5.5	18.8 ± 13.2	0
Postprandial	66.3 ± 15.6	6.9 ± 6.8	27.1 ± 15.2	0

Note: 3-cpm - three cycles per minute

Table 2 Results of ^{13}C-octanoic acid breath test (half-life of elimination in minutes) in ten healthy adult volunteers.

^{13}C-OABT	Mean	Std. Dev.	Median	IQR
Solid test meal	136	10.5	136	135–143
Semi-solid test meal	123	16	121	106–135.5

Note: ^{13}C-OABT – ^{13}C-octanoic acid breath test; Std. Dev. – standard deviation; IQR – inter-quartile range

Table 3 Results of ^{13}C-octanoic acid breath test (half-life of elimination in minutes) and EGG recording in Helicobacter pylori positive and negative healthy adult subjects.

Parameter	Fasting EGG 3-cpm (in per cent activity)	Postprandial EGG 3-cpm (in per cent activity)	^{13}C-OABT using a solid test meal (in minutes)	^{13}C-OABT using a semi-solid test meal (in minutes)
Helicobacter pylori positive subjects	65.3 ± 14.3	57.3 ± 8.1	141.5 ± 8	111.5 ± 8
Helicobacter pylori negative subjects	80.3 ± 17.2	75.3 ± 16.7	131 ± 10	112 ± 8

Note: 3-cpm - three cycles per minute

comprise ≥ 70 % of recording time. This 70% value is based on 4 studies that had lower limits (mean minus 2 SD) of 100, 58, 65 and 79 % [10,35, 43,48]. Neither these studies nor the document of the American Motility Society consider the Helicobacter pylori status of healthy subjects. This issue still remains rather controversial. The possible impact of Helicobacter pylori infection on EGG is discussed below.

EGG (recording of 30–60 min) is appropriate and produces reliable and predictable results [33]. We are aware of some possible limits of our study. Frequency analysis of the gastric slow waves exhibits only good to moderate reproducibility [23]. Short-term reproducibility of the postprandial time share of normogastria showed 86% agreement [23]. We did not evaluate the postprandial-to-fasting power ratio [55], frequency dynamics are considered to be a more reliable EGG parameter by some authors [38,39]. In a 24-hour EGG recording in healthy volunteers the gastric slow-wave rhythm is omnipresent but short periods of tachygastria could be found (not associated with any symptoms). A stable dominant frequency (for > 60 % of the time) was found only in one quarter of healthy volunteers. Dominant frequency varies during the day (maximum frequency at midday and minimum frequency during the night) [36]. All our EGG recordings were performed in the morning.

The possible relationship between EGG and gastric emptying also remains controversial [2,27,28,39, 50]. There could probably be a difference between healthy status and disease (i.e. diabetes mellitus, systemic sclerosis, functional dyspepsia, gastrectomy etc.). We have found a significant negative correlation between the half-life of elimination in ^{13}C-octanoic acid breath test (using a solid test meal) and a 3-cpm percent activity in postprandial EGG recording. Similar results in healthy subjects were also published by Hongo et al [22]. All postprandial peristalsis, gastric contractile force were reduced and gastric emptying delayed in elderly compared to young healthy volunteers. The ^{13}C-acetate breath test, another test of gastric emptying, was used in that study [51]. However, other studies found no age or gender related difference in EGG recordings [33,54]. In an experimental setting in dogs, gastric emptying correlated with the strength of gastric contractions in a frequency range identical to that of the gastric slow waves (major parameter of gastric myoelectrical activity) [61].

A lot of papers on EGG and gastric emptying in miscellaneous diseases have been published. Functional dyspepsia represents the most controversial issue in this aspect.

A high proportion of adult patients with functional dyspepsia (up to 60 %) had delayed gastric emptying (assessed by scintigraphy) and abnormalities in gastric myoelectrical activity [35, 47]. Parkman et al [45] studied EGG and solid-phase gastric emptying scintigraphy in functional dyspepsia. The EGG was abnormal in 11/22 (50 %) patients with delayed gastric emptying compared with 11/50 (22 %) with normal gastric emptying. The total symptom scores were higher in patients with both delayed gastric emptying and abnormal EGG [45]. 60 % of 30 children with functional dyspepsia had either slow gastric emptying (47 %) or abnormal EGG (50 %). Gastric emptying negatively correlated with fasting bradygastria. Gastric emptying was delayed in 73 % of patients with an abnormal EGG but was slow in only 20 % of subjects with normal EGG [17]. Van der Voort et al [59] investigated functional dyspepsia, irritable bowel syndrome and healthy controls. Disturbed gastric emptying correlated with a lack of postprandial increase in the EGG amplitude. Prokinetics (erythromycin) improved both gastric emptying and gastric electrical activity [59]. Gastric slow waves correlated negatively with gastric emptying (assessed by radionuclide scintigraphy) in functional dyspepsia according to another study [62]. However, negative studies in functional dyspepsia have also been published. EGG and gastric emptying scintigraphy did not correlate in children with vomiting and/or abdominal pain [1].

EGG values obtained in type-2 diabetics did not correlate with simultaneous radionuclide scintigraphy (40 % with delayed gastric emptying) [48]. Cucchiara et al [14] found a significant inverse correlation between gastric emptying rate and fed-to-fasting

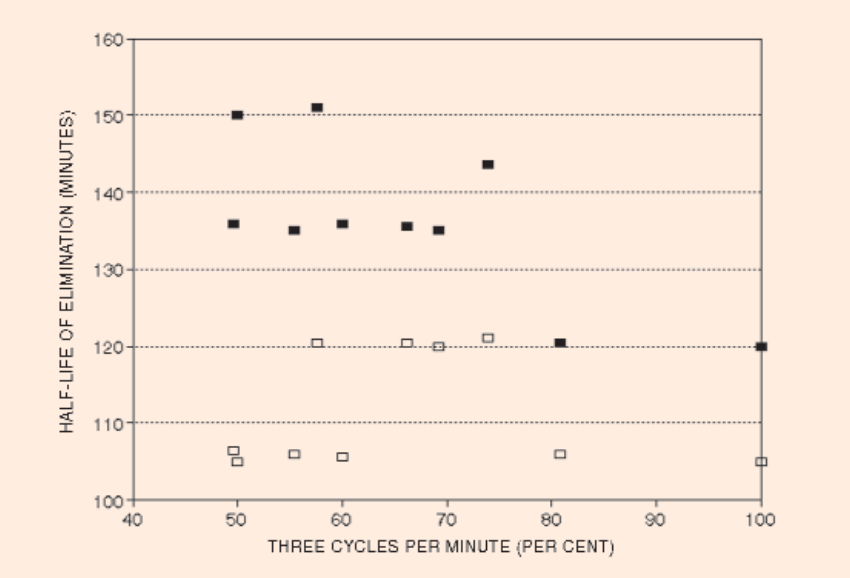

Figure
Results of ^{13}C-octanoic acid breath test (half-life of elimination in minutes) and electrogastrography (postprandial recording: three cycles per minutes in per cent) in ten healthy volunteers.
Closed symbols - solid test meal, open symbols - semi-solid test meal used.

ratio of the dominant EGG power both in type-1 diabetic children and healthy control subjects. Gastric emptying was delayed in 26/40 (65 %) diabetics and EGG dysrhythmias were more frequent compared to healthy children. Even more there was a significant correlation between serum glycosylated haemoglobin (HbA_{1c}) and gastric emptying delay [14].

Adolescent patients with bulimia who complained of dyspeptic symptoms had EGG abnormalities and delayed gastric emptying (assessed by scintigraphy). These abnormalities were not found in anorexia nervosa [15].

Half of our healthy volunteers were Helicobacter pylori positive. That reflects the current prevalence of Helicobacter pylori in the Czech Republic (42 %) [5]. In this study Helicobacter pylori negative subjects had higher percent activity of a 3-cpm rhythm and faster gastric emptying of solids compared to Helicobacter pylori positive persons. However, this difference was not statistically significant, probably due to a limited number of studied subjects. Possible influence of Helicobacter pylori infection on gastric myoelectrical activity has been studied intensively [4,24,25]. However, this issue remains controversial. Several papers have been published with both positive [34,52] and negative results [37]. Miyaji et al [40] found that gastric emptying, antral myoelectric activity and symptom scores in functional dyspepsia were improved by the eradication of Helicobacter pylori. In a Polish study [57], EGG, antral manometry and gastric emptying (assessed by ultrasonographic measurement of antral diameter) were investigated in Helicobacter pylori positive subjects with functional dyspepsia before and 1 month after eradication therapy. EGG showed significant dysrhythmias (with tachygastria up to 25 %) before eradication. Antral manometry failed to exhibit gastric phase III of the migrating motor complex in 7/12 subjects before eradication but could be observed again in 7/10 patients 1 month after successful eradication. Authors concluded that changes in gastric electrical control activity and antral hypomobility were associated with Helicobacter pylori infection [57]. However, according to other studies published so far, eradication of Helicobacter pylori infection has no impact on gastric emptying in patients with functional dyspepsia [21,31,32]. Murakami et al [41] found that gastric emptying was significantly delayed in functional dyspepsia compared to healthy control subjects but with no difference between Helicobacter pylori positive and negative persons.

In conclusion, EGG and gastric emptying rate, assessed by ^{13}C-octanoic acid breath test, are suitable non-invasive complementary methods to investigate the motor function of the stomach. The major parameters, 3-cpm rhythm (in EGG) and half-life of elimination (in ^{13}C-octanoic acid breath test) mutually correlate in healthy subjects.

The study was supported by research project MZO 00179906 from the Ministry of Health of the Czech Republic.

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