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Early steps of an alternative test meal for gastric emptying scintigraphy

Početni stadijumi razvoja alternativnog test-obroka za scintigrafiju pražnjenja želuca

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Abstract

Background/Aim. Gastric emptying (GE) scintigraphy provides a physiologic and noninvasive measurement of GE. Although GE scintigraphy has been standardized, preparing a meal is still complex and not practical in daily routine. The aim of the study was to prepare a simple, practical, and easily standardizable semisolid meal and investigate its role in estimating the GE function in of rabbits. **Methods.** In the first part of the study (basal condition), the mixture of the macroaggregated albumin (MAA) labeled with 37 MBq (1 mCi) of technetium-99m (^{99m}Tc) and 40 g of barium sulfate (1g/mL) was applied to animals *via* a nasogastric catheter. A series of images (frame/min, 60 min) in the anterior and posterior projections were dynamically acquired, and the motion was corrected after the radiopharmaceutical application. A few days later, the same rabbits were scanned under the same protocol after a 1 mg atropine injection to simulate gastroparesis condition. Eleven rabbits were included according to inclusion and exclusion criteria, and a total of twenty-two imaging data sets were analyzed for quantification. **Results.** In the basal study, total counts of the mixture decreased from 87,800.83 ± 12,622.76 to 42,733.14 ± 6,591.53 at 30 min and to 13,684.19 ± 1,774.90 at 60 min, and these decreases were statistically significant (p = 0.003). Emptying percentages were 51.39 ± 0.78% at 30 min and 84.32 ± 1.56 at 60 min and were statistically significant (p = 0.003). After intravascular atropine sulfate injection, total counts of the mixture decreased from 84,508.78 ± 11,871.48 to 64,995.18 ± 9,298 at 30 min and to 53,507.17 ± 7,258.98 at 60 min, and these decreases were statistically significant (p = 0.003). Emptying percentages were 23.10 ± 1.11% at 30 min and 36.63 ± 1.42 at 60 min and were statistically significant (p = 0.003). The difference between basal and post-atropine sulfate gastric emptying percentage at 30th (p = 0.003) and 60th (p = 0.003) min was statistically significant. **Conclusion.** The meal, used in this study, is non-nutrient, fatty-free, and semisolid and is easy to prepare and administer. Due to its semisolid nature, it offers a chance to evaluate the quantification of regional and total GE as well as the separate roles of the fundus and antrum.

Key words:
gastric emptying; gastroparesis; meals; rabbits; radionuclide imaging.

Apstrakt

Uvod/Cilj. Scintigrafija pražnjenja želuca (GE) obezbeđuje fiziološko i neinvazivno merenje GE. Iako je scintigrafija GE standardizovana, priprema obroka je i dalje složena i nije praktična u svakodnevnoj praksi. Cilj studije bio je da se pripremi jednostavan, praktičan i lako standardizovan polučvrst obrok i ispita njegova uloga u proceni funkcije GE kod zečeva. **Metode.** U prvom delu studije, mešavina mikroagregata albumina (MAA), obeleženog sa 37 MBq (1 mCi) tehnecijuma-99m (^{99m}Tc) i 40 g barijum sulfata (1 g/mL) davana je životinjama putem nazogastričnog katetera. Dinamska studija (*frame*/min, 60 min) je rađena neposredno nakon davanja obeleženog obroka u anteriornoj i posteriornoj projekciji i korigovana na pokretanje. Nekoliko dana kasnije, isti zečevi su skenirani pod istim protokolom nakon injekcije atropina od 1 mg da bi se simuliralo stanje gastropareze. Ukupno 11 zečeva je uključeno u skladu sa kriterijumima za uključivanje i isključenje, a ukupno 22 studije su analizirane za kvantifikaciju. **Rezultati.** U studiji pod bazalnim uslovima ukupan broj prikupljenih impulsa smanjio se sa 87 800,83 ± 12 622,76 na 42 733,14 ± 6591,53 nakon 30 min i na 13 684,19 ± 1 774,90 nakon 60 min i ova smanjenja bila su statistički značajna (p = 0,03). Procenti pražnjenja iznosili su 51,39 ± 0,78% nakon 30 min i 84,32 ± 1,56 nakon 60 min i bili su statistički značajni (p = 0,003). Nakon injekcije atropin sulfata, ukupan broj prikupljenih impulsa smanjio se sa 84 508,78 ± 11 871,48 na 64 995,18 ± 92 98 nakon 30 min i na 53 507,17 ± 7 258,98 nakon 60 min i ova smanjenja bila su

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statistički značajna (p = 0,003). Procenti pražnjenja iznosili su 23,10 ± 1,11% nakon 30 min i 36,63 ± 1,42% nakon 60 min i bili su statistički značajni (p = 0,003). Razlika između GE u prvom delu studije i posle primene atropin sulfata u 30. min i 60. min bila je statistički značajna (p = 0,003 u oba vremena). **Zaključak.** Obrok, primenjen u ovoj studiji, nije hranljiv, polučvrst je, bez masnoća i lak za pripremu. Zahvaljujući njegovoj polučvrstoj konzistenciji, pruža priliku da se kvantifikuje regionalno i ukupno GE, kao i procene uloge fundusa i antruma.

Ključne reči:
želudac, pražnjenje; gastropareza; obroci; zečevi; radioizotopsko snimanje.

Introduction

Gastroparesis is a term to describe delayed gastric emptying (GE), and patients often present with complaints of dyspepsia, which can be defined as any discomfort in the upper abdomen [1]. Although a less invasive technique such as wireless capsules has been used lately, placement of a tube or catheter-based probe within the gastrointestinal tract to measure pressure, electrical signal, or pH are general motility studies [2]. In contrast to probe methods, GE scintigraphy is performed with a radiolabeled meal so that the counts measured by the gamma camera are directly proportional to the volume of the meal in the stomach [3, 4]. Therefore, GE scintigraphy provides a physiologic and noninvasive measurement of GE without the need for geometric assumptions about the shape of the stomach. The method is quantifiable because the counts measured by scintigraphy correlate directly with the volume of the meal remaining in the stomach. Besides, compared with radiographic methods, scintigraphy involves low radiation exposure and uses commonly ingested foods rather than radiopaque markers [5].

Since the standard breakfast of ordinary food labeled with chromium-51 was used for GE scintigraphy in 1966, the importance of the meal used to obtain accurate results has been recognized over time. The content of the meal used is one of the most important variables needing standardization because GE depends on meal composition [3]. Chicken liver, pancakes, cheese, milk, oatmeal, honey buns, corn flakes and milk, peanut butter sandwiches, egg salad sandwiches, egg burritos, and McDonald's Egg McMuffins were used as test meals. In addition, different approaches for radionuclide labeling and adding time (before and after cooking) were observed in the literature [6].

In the "Consensus Recommendations for Gastric Emptying Scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine" by Abell et al. [3], it was proposed to use the most universally acceptable meal described by Tougas et al. [4]. One hundred twenty-three normal subjects from 11 medical institutions in the United States, Canada, and Europe were studied by Tougas et al. [4] in their multi-institutional protocol. The meal has a caloric value of 255 kcal (nutritional composition: 72% carbohydrates, 24% protein, 2% fat, and 2% fiber) that consists of a scrambled egg substitute (120 g EggBeater, 60 kcal, equivalent to the volume of two large eggs), two slices of bread (120 kcal), strawberry jam (30 g, 75 kcal) and water (120 mL). In addition, imaging was performed in the anterior and posterior projections at four time points (0, 1, 2, and 4 h), causing patients to stay in nuclear medicine clinics. Although above mentioned low-fat test meal was an important step in GE scintigraphy, preparation of this standardized meal is still complex and not easy from a practical point of view in daily routine. In addition, alternative meals must be considered for patients with egg allergies or intolerance to eggs, patients with gluten-sensitive enteropathy, and patients who report symptom exacerbations after eating lipid-rich foods [3]. Researchers have recommended adding butter (10 g) to the low-fat meal. Additionally, others have proposed Liquid Ensure (Abbott Laboratories, Abbott Park, IL) nutrient supplement or an oatmeal meal [3, 7]. However, it is essential to generate specific normal databases for these alternative meals before clinical utilization. Solid foods and fatty nutrients empty more slowly compared to liquids and foods containing proteins or carbohydrates. As a result, caloric ingredients and the form of the food can affect GE [8–10]. Therefore, both solid and liquid GE studies play an important role in assessing patients with upper gastrointestinal symptoms. Since measurement of simple total GE is often insufficient to explain the complaints of a patient with upper gastrointestinal symptoms, the evaluation of separate roles of the fundus and the antrum seems to be necessary [11]. Consequently, there is a need for an inexpensive, easily prepared meal and a relatively shorter study duration to evaluate both solid and liquid phases of GE in patients with upper gastrointestinal symptoms. In our study, we used a non-nutrient, semisolid meal consisting of technetium-99m (^{99m}Tc) macroaggregated albumin (^{99m}Tc-MAA) mixed with barium sulfate, which may be an alternative to the most universally accepted low-fat, solid meal. Although there are studies using barium to evaluate GE in animals radiographically, to the best of our knowledge, this is the first study using barium mixed with ^{99m}Tc-MAA to evaluate GE in animals scintigraphically. The aim of the study was to establish a practical and easily standardizable semisolid meal and investigate its role in estimating the GE functions of rabbits.

Methods

Animals, meal, and administration

The study was performed between July and December 2016. A total of 14 male, three to four months old, New Zealand white rabbits weighing between 2,000 to 2,500 g (mean: 2,215 g) were included in this study. Being healthy, weighing 2,000–3,000 gr, and three to six months old were the inclusion criteria. Rabbits used in prior experiments or showing signs of illness or rabbits unsuitable for image acquisition and data quantification due to extreme motion were the exclusion criteria. Eleven rabbits were included according to inclusion and exclusion criteria, and a total of 22 imaging data sets were analyzed for quantification. We preferred to use ^{99m}Tc-MAA instead of ^{99m}Tc-sulfur colloid due to our clinical logistics. In the first part of the study (basal study, without atropine sulfate injection), the MAA (Makro-Albumon®, Medi-Radiopharma, Budapest, Hungary) labeled with 37 mBq (1 mCi) of ^{99m}Tc (Molybdenum-99/Technetium-99m generator, Kamrusepa/Samyoung, Turkey) was mixed with 40 g/40 mL barium sulfate (1 g/mL, Radyobarit solution, Recordati Drug Company, Italy) by using a vortex mixer and the mixture was applied to animals *via* a nasogastric catheter. Rabbits were stabilized, but in order not to affect physiological gastric functions, the rabbits were not anesthetized during the dynamic acquisition of images. A few days later, the same rabbits were scanned under the same protocol immediately after 1 mg atropine sulfate (1 mg/1 mL, Biofarma, Turkey) injection into a marginal ear vein to simulate gastroparesis condition. This dosage was determined by a pilot study, in which the minimum standard dose of atropine necessary to produce a significant delay in GE was established. The Local Ethics Committee for animal studies of the Gülhane Military Medical Academy approved our study protocol (2014/28-14/173).

Acquisition and instrumentation

The subjects were fixed on the wooden plate in a prone position on the imaging table of a two-detector gamma camera (GE, Millennium VG, USA) equipped with a low-energy all-purpose (LEAP) collimator, using a 15% window centered over the 140 keV photopeak in a 128 × 128 matrix. A series of images (frame/min, 60 min) in the anterior and posterior projections were dynamically acquired and motion corrected after the radiopharmaceutical application.

Image evaluation

Depth-corrected total gastric counts [geometric mean: $\sqrt{anterior\ counts\ x\ posterior\ counts}$] from 1st, 30th, and 60th frames of the dynamic images were calculated. Decay correction was also performed. The emptying percent for 30th min and 60th min was calculated *via* the following formula:

[(1st frame total gastric counts) – (30th or 60th frame total gastric counts) / 1st frame total gastric counts] X 100.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). The Wilcoxon signed-rank test was used to evaluate the significance of the difference between the calculations. Statistical analysis was performed using the IBM SPSS Statistics for Macintosh, Version 26.0. (Armonk, NY: IBM Corp.). Differences were considered significant at $p < 0.05$.

Results

When dynamic images were evaluated qualitatively, the mixture of ^{99m}Tc-MAA and barium sulfate was emptied from the stomach regularly. Total counts decreased from 87,800.83 ± 12,622.76 (a) to 42,733.14 ± 6,591.53 (b) at 30 min and to 13,684.19 ± 1,774.90 (c) at 60 min and these decreases were statistically significant (a to b: $p = 0.003$, a to c: $p = 0.003$, and b to c: $p = 0.003$). GE percentages were 51.39 ± 0.78% at 30 min and 84.32 ± 1.56% at 60 min (Figure 1) and were statistically significant (30 to 60 min: $p = 0.003$). Percentages of gastric retention were 48.60 ± 0.23% at 30 min and 15.67 ± 0.47% at 60 min (Figure 2) and were statistically significant (30 min to 60 min: $p = 0.003$).

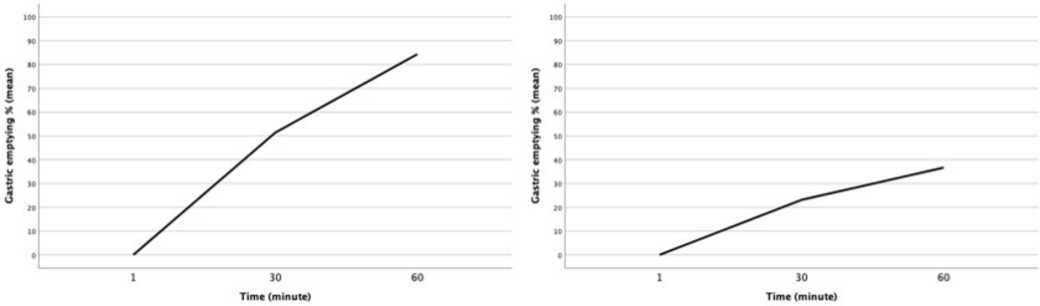

Fig. 1− The line chart shows the percentage of the mean gastric emptying changing over time in the basal study – without atropine sulfate injection (left) and after atropine sulfate injection (right).

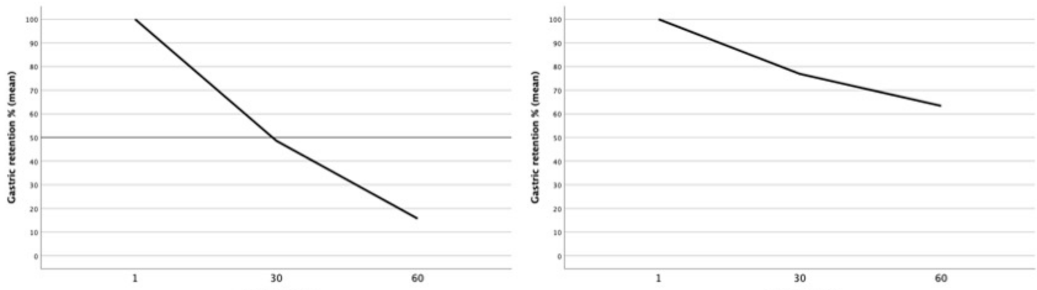

Fig. 2 − The line chart shows the percentage of the mean gastric retention changing over time in the basal study – without atropine sulfate injection (left) and after atropine sulfate injection (right).

After intravascular atropine sulfate injection, the mixture of ^{99m}Tc-MAA and barium sulfate was emptied from the stomach regularly but more slowly. Total counts decreased from 84,508.78 ± 11,871.48 (d) to 64,995.18 ± 9,298.39 (e) at 30 min and to 53,507.17 ± 7,258.98 (f) at 60 min and these decreases were statistically significant (d to e: p = 0.003, d to f: p = 0.003, and e to f: p = 0.003). Emptying percents were 23.10 ± 1.11% at 30 min and 36.63 ± 1.42% at 60 min (Figure 1) and were statistically significant (30 to 60 min: p = 0.003). The difference between basal and post-atropine sulfate GE percentage at 30th (p = 0.003) and 60th min (p = 0.003) was statistically significant. Gastric retention percentages were 76.89 ± 0.33% at 30 min and 63.36 ± 0.42% at 60 min (Figure 2) and were statistically significant (30 min to 60 min: p = 0.003).

Irregular regions of interest close to the stomach were manually defined to analyze the total gastric counts on the dynamic image set from anterior and posterior projections (Figure 3).

semisolid mixture was delivered *via* a nasogastric catheter and rapidly dispersed in the stomach.

In GE studies of humans, solid foods transfer from the posteriorly located fundus into the more anteriorly located antrum, and measured counts increase during the anterior projection imaging. To avoid this, dual projection imaging from the anterior and posterior is acquired, and depth-related attenuation correction is performed by calculating the geometric mean. Therefore, the geometric means of decay corrected counts from anterior and posterior projections were used in our study.

Peristaltic contractions transform large solids into smaller 1–2 mm particles with the participation of gastric digestive fluids in the process called 'trituration'. Thus, they discharge monoexponentially at the same rate as the liquids and more rapidly than solids, without lag phase [5, 12]. The liquids require no 'trituration', and liquid-phase GE remained normal until gastroparesis was at an advanced stage. The liquids were less sensitive than solid foods for detecting

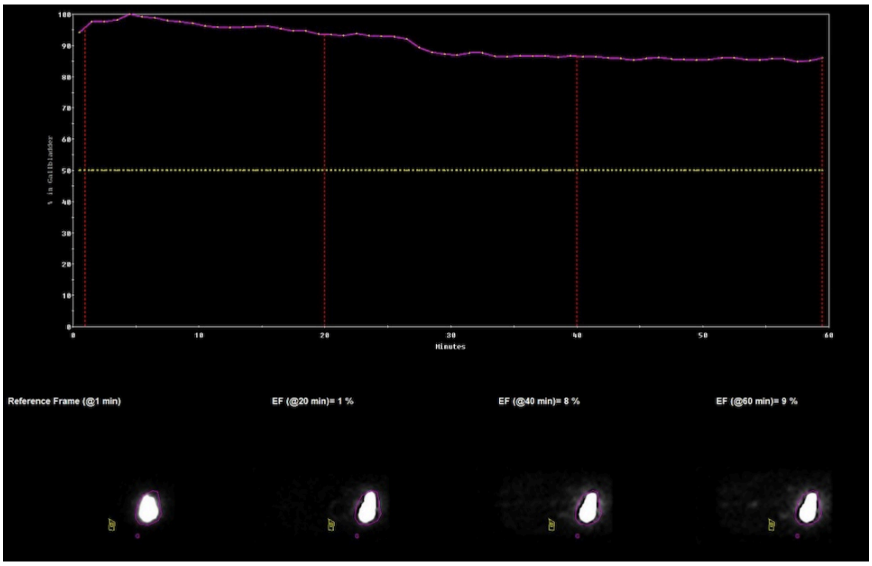

Fig. 3 − An example image dataset of the gastric emptying study in gastroparesis condition after atropine sulfate injection.

Discussion

We prepared a semisolid meal and administered it to rabbits *via* nasogastric catheter to simulate normal gastric function (without atropine sulfate injection) and gastroparesis condition (after atropine sulfate injection) separately and calculated GE rates. Our approach for GE scintigraphy is completely different from the most universally acceptable meal and the protocol, which has the largest normative database [3, 4].

Unlike liquids, solid foods are principally localized in the fundus, referred to as the ‘accommodation response’, and continual slow fundal contractions transfer them to the antrum [5]. Initial and selective localization of solid foods in the fundus can be detected in the first images of a GE study. However, in our study, it was not possible to evaluate the ‘accommodation response’ of the stomach since our

early gastroparesis [13], and in order to detect gastroparesis, solid-phase GE scintigraphy is still in use [3]. Conversely, postprandial fullness and early satiety are associated with delayed GE of the liquids [8]. Thus, the liquid-phase GE studies complement solid-phase GE studies because there is a relationship between delayed GE of both and symptoms of postprandial fullness, nausea, and vomiting [5]. In combined dual-isotope solid- and liquid-phase GE, emptying of liquids may be abnormal when the emptying of solids is normal. In one study, 26% of patients were reported to have normal solid-phase GE but delayed liquid-phase GE [14]. Therefore, combined dual-isotope solid- and liquid-phase GE studies are necessary to determine the patients with gastroparesis. For this reason, a semisolid meal with the additional advantage of a low radiation dose may be more convenient and practical for evaluating these patients. Hence, we have mixed ^{99m}Tc-MAA with barium sulfate to prepare an easily standardizable non-nutrient semisolid meal. Besides, it has been suggested that a non-nutrient, liquid GE study may detect fundal gastric dysmotility [15].

There were no adopted standards for performing GE scintigraphy until a consensus recommendation of a solid-meal GE test, which can provide clinicians with standardized results, was published in 2007 [3]. Normal values were settled not only for the meal but also for the method of acquiring and processing the images in this consensus report; the patients were instructed to stop using medications that affect GE and fasting. Furthermore, since GE studies are complex, the consensus group has identified the limitations of their suggestions, one of them being a need for necessary information on other substitute meals [5]. Our semisolid meal may have a chance as a candidate for a substitute meal in this arena.

The consensus group suggested using a low-fat, solid meal based on normative data from a large multicenter study [4]. The meal comprises 120 g (4 oz) of Eggbeaters (ConAgra Foods) or a generic liquid egg-white equivalent, mixed with 18.5–37.0 MBq (0.5–1.0 mCi) of ^{99m}Tc-sulfur colloid, two slices of white bread, 30 g of strawberry jam, and 120 mL of water. The total energy of the meal is 255 kcal (72% carbohydrates, 24% protein, 2% fat, and 2% fiber). During cooking, ^{99m}Tc-sulfur colloid binds to the egg white. This recipe is not easy to prepare and not practical in the daily routine of a nuclear medicine department. Therefore, we have suggested using the ^{99m}Tc-MAA with a barium sulfate mixture. Since both of them are imaging agents, they are ready to prepare, and the mixture can be administered to the patients easily *via* the oral route. Besides, this semisolid meal may be a useful alternative for patients with egg allergies or intolerance to eggs and patients with gluten-sensitive enteropathy.

The early phase (0–2 h) of a solid GE study mirrors principally fundal function, and the later phase (2–4 h) projects mainly trituration and transfer of the food into the duodenum. Although studies vary in duration from as short as 60 min to as long as 4 h, studies have shown that lengthening the scan to 4 h increases the detection rate of delayed gastric discharge [5, 16]. In the 'Consensus Recommendations for Gastric Emptying Scintigraphy' published by Abell et al. [3], the suggested time points for acquisition of GE scintigraphy images are 0, 60, 120, and 240 min for solid-phase GE scintigraphy. In one study by Guo et al. [16], it was suggested that the 3 h period might be as sensitive as a 4 h study in detecting delayed GE. Further, in another study by Hou et al. [17], it was shown that the 3-h time point is nearly comparable to the 4 h value in detecting patients with delayed GE. Consequently, it may be possible to shorten the duration of the GE study. In contrast to previous studies, we have dynamically imaged the subjects for 60 min to observe the activity passage. Since our meal is semisolid, it has acted as partially liquid, and, therefore, almost half of the activity emptied from the stomach in 30 min. According to our results, our semisolid meal seems to have the potential to give earlier results than the suggested solid meal.

There are incongruities in the quantitative data reported. It has been reported that half-times ($T_{1/2}$ values) of emptying may be potentially less accurate than percentages of retention measured at constant moments in individuals with very prolonged emptying. Furthermore, extrapolation is needed to compute the $T_{1/2}$ value if it was not reached during the study [3]. Studies have shown that percentage of gastric retention has greater sensitivity [10], and it is the most reproducible [11]. Hence, we calculated the percentage of GE and gastric retention at two different time points in our study population.

Abnormal intragastric distribution patterns have also been associated with dyspeptic symptoms due to the separate roles of the fundus and antrum. After the ingestion of solid food, most of it is localized in the upper half of the stomach. This fundal accommodation is a physiologic response to an increase in gastric volume without increasing intragastric pressure. Impaired fundal accommodation can cause dyspeptic symptoms [18]. The invasive barostat testing is the best direct measurement of fundal accommodation [19]; a less invasive water load test can also be used to evaluate the relationship between impaired accommodation and dyspeptic symptoms. Fundal accommodation is best observed in the early images of routine planar GE scintigraphy; the joint report of two different societies suggested evaluating the images for the presence of an abnormal accommodation response [3]. The intragastric distribution of the test meal between the fundus and antrum can be easily evaluated by scintigraphy imaging. However, since our semisolid meal was administered *via* a nasogastric catheter, we could not evaluate the fundal accommodation. If it is administered *via* the oral route, the semisolid properties of our agent may provide information non-invasively regarding the fundal and antral intragastric distribution of activity and quantification of regional GE in humans.

GE depends on the composition of the meal. Solid foods empty more slowly than fluids, and easily digestible soft solids empty more rapidly than solid foods [8]. Further, the emptying of fatty nutrients is slow compared to proteins or carbohydrates. After the inlet of fat nutrients into the duodenum, receptors in the duodenum cause a duodenogastric interaction that induces cholecystokinin release and, as a result, slow entry of the meal into the duodenum occurs [9, 10]. The caloric ingredient and volume of the test meal will also affect GE [3]. Besides, since water drinking has been shown to hinder antral motility after a caloric meal [14], further studies of the physiologic and clinical significance of using a non-alimentary, liquid meal are needed. For this reason, our semisolid mixture is non-nutrient and fat- and calorie-free.

Consensus on performing a solid-phase GE scintigraphy test for clinical practice, based on readily available technology and normative data, which can provide clinicians with standardized results, has been available since 2007 [3, 5, 20].

Study limitations

In this preliminary animal study, the study population was not large enough to get definite conclusions. The mechanisms conducting gastrointestinal motility in herbivores can be completely different from those in humans, and, therefore, GE scintigraphy results in animals may not reflect the actual physiology in humans. Further, the validity of ^{99m}Tc-MAA mixed barium sulfate as a test meal may not be definitive and need improvement in a large-scale animal study with additional control groups. It would be very appropriate to compare the GE of ^{99m}Tc-MAA mixed barium sulfate with the universally accepted caloric solid test meal. However, ingestion of the universally acceptable caloric test meal by subjects and adjusting the volume of the caloric solid test meal suitable for subjects are the challenges of this process. Another limitation of this study is the significant need to test the labeling stability of ^{99m}Tc-MAA mixed barium sulfate in an acid medium.

Conclusion

The meal used in this study is non-nutrient, fatty-free, and semisolid and is easy to prepare and administer. It seems to have a chance to evaluate the quantification of regional and total GE as well as the separate roles of the fundus and antrum due to its semisolid nature. There are many reasons for the current diversity of imaging and analysis of GE scintigraphy protocols, such as an individual center's meal and analysis preferences, different camera and computer systems, scheduling constraints, and processing software. However, the caloric content and volume of the test meal and consuming water will also affect GE and are important factors to consider. Therefore, further studies of the physiologic and clinical significance of using a non-alimentary, liquid meal are needed. In this preliminary animal study, we aimed to develop the early steps of an alternative approach to the consensus for solid-phase GE scintigraphy, which needs to be improved in larger-scale animal studies.

Conflict of interest

The authors declare no conflict of interest associated with this publication. Additionally, there has been no financial support.

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