Direct comparison of solid-phase gastric emptying times assessed by means of a carbon isotope–labeled sodium acetate breath test and technetium Tc 99m albumin colloid radioscintigraphy in healthy cats

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Objective—To directly compare solid-phase gastric emptying times assessed by means of a [^{13}C]sodium acetate breath test ([^{13}C]-SABT) and technetium Tc 99m albumin colloid radioscintigraphy (^{99m}Tc-ACR) in healthy cats.

Animals—12 healthy cats.

Procedure—After ingestion of a test meal containing 50 mg of [^{13}C]sodium acetate and 250 MBq of ^{99m}Tc-albumin colloid, each cat underwent simultaneous [^{13}C]-SABT and ^{99m}Tc-ACR on 2 consecutive days. Breath samples and scintigrams were acquired at 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 480, and 600 minutes after meal ingestion. Quartiles of gastric emptying (25%, 50%, and 75%) were calculated for breath test analysis by use of the area under the curve of the ^{13}C:^{12}C ratio. Quartiles of gastric emptying times were extrapolated from the scintigraphic findings by beans of nonlinear curve regression analysis.

Results—Mean ± SD gastric half-emptying (50%) times obtained with [^{13}C]-SABT and ^{99m}Tc-ACR, were 239 ± 28 minutes and 276 ± 59 minutes, respectively. A 2-way repeated-measures ANOVA revealed that mean gastric emptying times determined with [^{13}C]-SABT and ^{99m}Tc-ACR differed significantly. For the stages of gastric emptying, Pearson correlation between the 2 methods was good at 25% (r = 0.655) and weak at 50% (r = 0.588) and 75% (r = 0.566)of gastric emptying.

Conclusions and Clinical Relevance—Results indicated that the [^{13}C]-SABT can be a valid alternative to ^{99m}Tc-ACR in healthy cats; it was easy to perform, was tolerated well by the cats, and had acceptable correlation to scintigraphic findings at gastric emptying of 25%, 50% and 75%. Studies in cats with delayed gastric emptying will be needed to verify the validity of the [^{13}C]-SABT. (*Am J Vet Res* 2014;75:648–652)

Accurate measurement of gastric emptying is rarely performed in cats, unlike in humans and dogs. This might be partially due to the fact that no routine tool or test is available to accurately assess gastric emptying in a clinical setting or that serial sample collection of blood, intestinal content, or breath is more difficult in cats than in humans and other companion animal species. Hence, data on physiologic feline gastric emptying times are scarce, and techniques used in the past either provide crude estimates of gastric emptying (radiographic assessment of the passage of liquid barium[1]), are correlated with interdigestive motility rather than physiologic gastric emptying (evaluation of the transit of barium-impregnated polyethylene spheres[2–4]), or are difficult to use in a routine clinical environment (radioscintigraphy[5–7]). Test meals used have been of variable composition, making comparison of feline gastric emptying times among studies difficult. Thus, the clinical importance of gastric emptying disorders in cats remains unclear and might be largely underestimated. To our knowledge, there are few case reports regarding delayed gastric emptying in cats that have rare conditions such as pylorospasm,[8] hyperplastic gastropathy,[9] and dysautonomia.[10] Delayed or dysfunctional gastric

Abbreviations

[^{13}C]-SABT	[^{13}C]Sodium acetate breath test
^{99m}Tc-ACR	Technetium Tc 99m albumin colloid radioscintigraphy

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emptying might be suspected in conjunction with more common conditions like diabetes mellitus, pancreatitis, and inflammatory intestinal, hepatic, or biliary diseases; however, investigations of gastric motility in cats with these disorders have not been performed to date.

For some years, radiolabeled carbon breath tests have been used successfully in people[11] and companion animals.[12,13] Such breath tests have recently been introduced for use in cats[14] as an alternative method for measurement of gastric emptying times because they are noninvasive and do not involve the handling of radioactive isotopes. Breath tests involve the ingestion of a substance labeled with radioactive carbon (the stable isotope ^{13}C), which is absorbed in the small intestine and then rapidly metabolized to $^{13}CO_2$ and exhaled. Thus, the increase in the ^{13}C:^{12}C ratio in breath samples correlates indirectly to gastric emptying. To our knowledge, breath tests have not been directly compared with gastric radioscintigraphy in cats; therefore, the diagnostic usefulness of such breath tests in this species has not been fully investigated. In humans, breath test results do not correlate well with radioscintigraphic findings,[15–17] but in horses[18] and dogs,[12] data obtained by these 2 methods have good correlation.

The purpose of the study reported here was to directly compare solid-phase gastric emptying times assessed by means of a [^{13}C]-SABT and ^{99m}Tc-ACR in healthy cats. The intent was to establish a new method for determination of gastric emptying times in cats, thereby providing a test that might be of clinical value.

Materials and Methods

Cats—Twelve domestic shorthair cats from the research and blood donor colony of the Small Animal Hospital, Justus-Liebig University, Giessen, were used. All cats were castrated males with a median age of 3 years (age range, 2 to 4 years) and a median weight of 5.3 kg (weight range, 4.5 to 5.9 kg). They were deemed healthy on the basis of the absence of clinical signs, absence of abnormal findings detected via physical examination, and unremarkable results of routine hematologic and biochemical analyses. Seven days prior to the start of the study, all cats were treated with fenbendazole (50 mg/kg) for 3 days.

Experimental procedures—Governmental ethical approval was obtained for the study. For each cat, [^{13}C]-SABT and ^{99m}Tc-ACR and were performed simultaneously on 2 consecutive days. The test meal provided to each cat at the start of each experiment consisted of commercially available canned cat food,[a] which was chosen because of its high palatability; 250 MBq of ^{99m}Tc and 50 mg of [^{13}C] sodium acetate[b] were added to each meal. The ^{99m}Tc was bound to a commercially available albumin colloid[c] to avoid absorption. The double-labeled meal was then mixed thoroughly with a household blender to ensure equal distribution of the additives.

After food was withheld for 12 hours, a baseline breath sample was collected from each cat before the test meal was provided. Breath sample collection involved use of an anesthetic face mask that was connected via a 2-way valve to a glass vial.[d] To obtain a breath sample, each cat was individually placed on an examination table in sternal or sitting position with minimal manual restraint. Thereafter, the test meal was offered to the cat. Immediately after consumption of the entire meal, a baseline scintigraphic image was obtained (0 minutes). For image acquisition, the conscious cat was placed on the collimator of a gamma camera[e] in sternal position (again with minimal manual restraint) for an acquisition time of 60 seconds. Subsequently, both breath samples and scintigraphic images were obtained 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 480, and 600 minutes after acquisition of the initial image. At all time points, a breath sample was obtained immediately after the scintigraphic image acquisition was completed, while the cat was still placed on the collimator of the gamma camera. In the periods between data collections, each cat was kept in a kennel holding area that was part of the radiation facilities. Each cat had access to water ad libitum during these periods; however, consumption of water was not assessed or measured.

The ^{13}C:^{12}C ratio in breath samples collected at each time point was determined within 14 days after collection; results of a pilot study had indicated that samples are stable for at least 14 days after collection (data not shown). Breath samples were analyzed in duplicate via gas chromatography with isotope ratio mass spectrometry. Ion currents consistent with the mass of ^{12}C (m/z 44) and ^{13}C (m/z 45) were measured against certified International Atomic Energy Agency reference material. To allow a Craig[19] correction for radiolabeled oxygen O 17 (^{17}O), radiolabeled oxygen O 18 (^{18}O; m/z, 46) was also determined. The $^{13}CO_2$:$^{12}CO_2$ ratio (or delta-over-baseline ^{13}C) was calculated with the integrated software.[f] The ratio of ^{13}C to ^{12}C was expressed in permille, which reflects the ^{13}C:^{12}C isotope ratio in relation to a primary reference isotope ratio (Pee Dee Belemnite [PDB] standard[19]). The total area under the curve was calculated over the 600-minute experimental period. Subsequently, quartiles of gastric emptying (25%, 50%, and 75%) were determined.

For analysis of scintigraphic images, the region of interest (stomach) was defined manually for each image on the basis of morphology, and all pixels within this region were counted automatically. Subsequently, the decay-corrected radioactivity counts were plotted against time. Gastric emptying times for different emptying stages (25%, 50%, and 75%) were determined by nonlinear regression analysis (**Figure 1**) with commercially available software.[g] The mathematical model was created with regard to the observation that after a lag phase, an approximately linear decrease of the radioactivity occurred (**Appendix**).

Data and statistical analysis—To assess intraassay (day-to-day) variation for each cat, the coefficient of variation was calculated for each method by means of a 2-way ANOVA with nested random factors. In addition, paired *t* tests were performed on scintigraphic data obtained on the 2 consecutive days (days 1 and 2) and on breath test data obtained on days 1 and 2 to test for systematic trends between the first and second replication. Because the intra-assay variation was found to be low (< 10%) and the paired *t* tests revealed no significant changes between day 1 and day 2 for either method (data not shown; all P values > 0.45), further

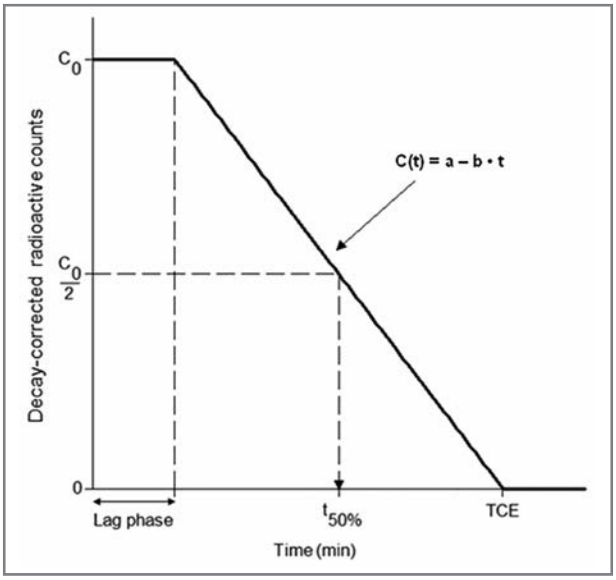

Figure 1—Nonlinear mathematical model developed to estimate solid-phase gastric emptying times for various stages of emptying in cats via ^{99m}Tc-ACR. After the lag phase, decay was approximately linear. C_0 = Radioactivity count at 0 minutes. $C_0/2$ = Radioactivity count at 0 minutes divided by 2 (half of the initial count). C(t) = Radioactivity count as a function of time. $t_{50\%}$ = Time at which gastric emptying was 50%. TCE = Time at which gastric emptying was complete.

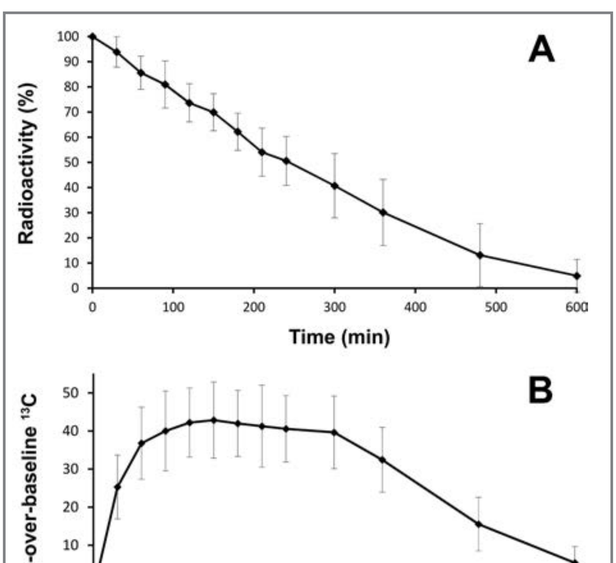

Figure 2—Gastric emptying in 12 healthy cats assessed via ^{99m}Tc-ACR (A) and a [^{13}C]-SABT (B) simultaneously after ingestion of a test meal containing 50 mg of [^{13}C]sodium acetate and 250 MBq of ^{99m}Tc-albumin colloid on 2 consecutive days (averaged data). A baseline breath sample was obtained prior to meal ingestion, and a baseline scintigram was obtained immediately after meal ingestion (at 0 minutes). Breath samples and scintigrams were acquired for analysis at 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 480, and 600 minutes after meal ingestion. The y-axis depicts decay-corrected radioactivity counts and the delta-over-baseline ^{13}C value (^{13}C:^{12}C ratio) in breath samples, respectively.

analyses were performed on means of the data from days 1 and 2 (designated as global means).

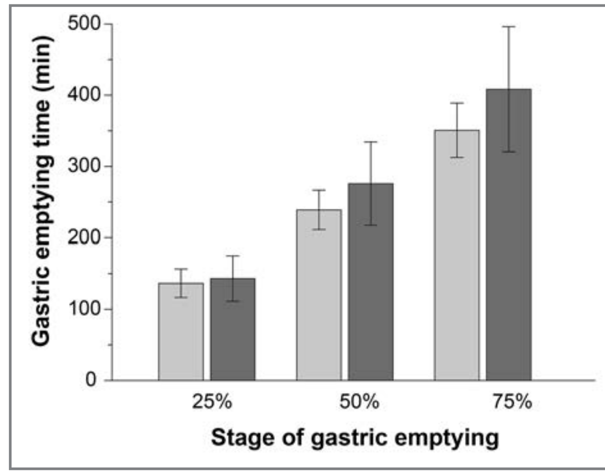

Figure 3—Mean ± SD gastric emptying times for various stages of emptying (25%, 50%, and 75%) in the 12 healthy cats in Figure 2 assessed via [^{13}C]-SABT (light gray bars) and ^{99m}Tc-ACR (dark gray bars).

A 2-way repeated-measures ANOVA incorporating the effects of method and stage of gastric emptying was performed to compare values of [^{13}C]-SABT and ^{99m}Tc-ACR for the 3 stages of gastric emptying (25%, 50%, and 75%). Additionally, the Pearson correlation coefficient between the 2 techniques was determined for each emptying stage. For all analyses, a value of $P < 0.05$ was considered significant.

Results

All cats accepted the test meal voluntarily and in its entirety (food was consumed within 1 to 3 minutes); hence, all measurements could be performed completely. There was no significant difference in time to complete consumption of test meals among cats or between days of performance of the experiments. The pattern of scintigraphic gastric emptying was approximately linear with a negligible lag phase in nearly all cats (**Figure 2**). Breath test analysis revealed a steady increase in $^{13}CO_2$ concentration with a maximum value attained at approximately 150 minutes after ingestion of the test meal. The global means (mean values calculated from both days' measurements) of gastric emptying times determined via the [^{13}C]-SABT and ^{99m}Tc-ACR were significantly ($P = 0.033$) different (**Figure 3**). There was a significant ($P < 0.001$) interaction between method and stage of gastric emptying (25%, 50%, or 75%), indicating increasing differences between the means determined by the 2 methods with increasing degree of emptying. For the stages of gastric emptying, the correlation between the 2 methods was good at 25% ($r = 0.655$; $P = 0.021$) and weak at 50% ($r = 0.588$, $P = 0.044$) and 75% ($r = 0.566$, $P = 0.055$).

Discussion

Gastric radioscintigraphy is generally accepted as the gold standard method to assess gastric emptying in many species.[20] Consequently, it has been recommended that all new methods should be compared against that technique. For humans, the Society of Nuclear Medicine has defined a standard protocol, and reference ranges derived from large study groups are available.[21] This is not the case in veterinary medicine; no standard protocols are recognized, and species-specific reference ranges have not been determined. Nonetheless, radioscintigraphy has been used to assess gastric emptying in various animal species, including dogs, cats, horses, rats, monkeys, and pigs.[20] Radioscintigraphy with ^{99m}Tc compounds (^{99m}Tc bound to pertechnetate,[12] diethylene triamine pentacetic acid,[22] sulfur colloid,[23] tin,[24] albumin colloid,[20] disofenin,[25] mebrofenin,[26] or resin beads[27]) has been used most frequently in animals. Although some authors recommend the use of mebrofenin or disofenin in small animals on the basis of data from efficiency experiments,[23] the present study indicated that ^{99m}Tc albumin colloid can be used in cats.

In humans, the [^{13}C]-SABT has been used successfully to measure gastric emptying.[28] In the present study, breath samples were collected from cats for 10 hours after feeding of a test meal because long periods of assessment have been shown to provide more accurate results.[29] Sample collection intervals were short, especially at the beginning of gastric emptying, but they could be prolonged to make the test easier to perform. The use of gas chromatography to measure the ^{13}C:^{12}C ratio in breath samples was ideal because only small volumes of exhaled air could be collected from the cats. However, the fact that gas chromatography might not be readily available outside a research environment might limit clinical use of the breath test. There was little variation in [^{13}C]-SABT results obtained from the cats in the present study between the 2 consecutive days on which experiments were conducted. This minor data variation between experiment days was consistent with findings for some companion animals (eg, horses[18]) but not for others (eg, dogs[12]). It is also interesting to note that overall, gastric emptying in cats is much slower than it is in dogs. Gastric half-emptying (50%) was achieved at approximately 4 hours after ingestion of a meal in the cats in the present study, whereas in another study[12] involving the same test protocol in dogs, gastric half-emptying was achieved at approximately 2.5 hours after ingestion of a meal. The reasons for the time difference might be purely physiologic or species related. However, the good reproducibility of gastric emptying times with both methods in the present study could also be attributable to the fact that cats seem less affected by the procedure than are dogs, making feline gastric emptying more constant. It is difficult to compare the results of the breath test performed in the present study with data reported in the veterinary medical literature because methods of determining gastric emptying times vary. For example, in a study in cats by Peachey et al,[14] peak CO_2 production was determined without further calculation of gastric emptying times and the mean time after meal ingestion to peak CO_2 production was approximately 60 minutes; in the present study, the mean time after meal ingestion to peak CO_2 production was approximately 150 minutes. In the present and previous studies, it was evident that gastric emptying is not complete at 300 minutes after ingestion of a meal in cats and, as the present study findings indicated, CO_2 concentration in breath samples starts to decrease between 300 and 600 minutes after meal ingestion.

To our knowledge, this is the first study in which direct and simultaneous comparison of gastric radioscintigraphy and a carbon C^{13} isotope–based breath test was performed in cats. It is interesting to note that the scintigraphic data indicated no clear lag phase for gastric emptying in most of the cats in the present study, as would be expected with solid-phase gastric emptying. This could be due to the type of food used in the study (the food had to be homogenized with the radioactive labels, and as a result was in a semisolid or paste-like form rather than chunks of food) or may be indicative of a species-specific pattern of gastric emptying. Technical difficulties related to the test meal seem less likely, considering that the same technique has been used in dogs, most of which had a demonstrable lag phase and a sigmoidal pattern of gastric emptying.[12] The mean gastric half-emptying times (50%) in the present study were 238 minutes (approx 4 hours) for [^{13}C]-SABT and 276 minutes (approx 4.5 hours) for ^{99m}Tc-ACR, which is longer than most published gastric emptying times for cats. Values at all examined time points did not differ significantly between methods. Correlation between methods (as determined by Pearson correlation coefficient) was good at the 25% stage of emptying and weak but acceptable at the 50% and 75% stages of emptying. These findings could be a result of the nature of the 2 methods: one (^{99m}Tc-ACR) is direct, whereas the other ([^{13}C]-SABT) is indirect. Evidently, for eventual clinical use, slightly different reference ranges will be needed depending on the technique used. Correlation could also decrease with ongoing gastric emptying, given that the individual variation (SD) of gastric emptying times appeared to increase over time. Nonetheless, the results of the correlation analysis between the 2 methods in cats indicated that the [^{13}C]-SABT can be a valid alternative to ^{99m}Tc-ACR, given that it was easy to perform and tolerated well by the cats in the present study. Findings of the present study also indicated that half-emptying times might not be the most appropriate time points to use as the only measure of gastric emptying in cats. Variation in half-emptying times among individual cats was detected and would have to be taken into account when interpreting gastric emptying results. Extrapolation of results of the present study to a clinical situation may be challenging, and further research in this field is necessary before the [^{13}C]-SABT can be used in a wider clinical context to assess gastric emptying of individual cats with disorders that might be associated with delays in gastric emptying.

a. a/d, Hill's Pet Nutrition Inc, Hamburg, Germany.
b. ^{1,13}C-sodium acetate, Sigma Aldrich Corp, Munich, Germany.
c. Solco-Nanocoll, Sorin-Biomedica, Munich, Germany.
d. Non-evacuated Exetainer, Labco Ltd, High Wycombe, Buckinghamshire, England.
e. Philips Gamma Diagnost Tomo, Philips Medical Systems, Hamburg, Germany
f. IonVantage 1.1, GV Instruments Ltd, Wythenshawe, Cheshire, England.
g. BMDPAR, BMDP Statistical Software, version 8.1, Statistical Solutions, Cork, Ireland.

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Appendix

Equations used to perform nonlinear curve fitting of scintigraphic data to estimate gastric emptying times at various emptying stages (25%, 50%, and 75%) in cats.

Different conditions were used depending on the section of the sigmoid emptying curve. The lag phase was defined as all time points (or x values; t) where no change or decreased radioactivity counts in relation to the initial count at 0 minutes (C_0) were observed. The linear decay phase (between the lag phase and the time of complete stomach emptying) was described as a simple linear curve based on the following equation:

$$C(t) = a - b \bullet t$$

where C(t) is the count as a function of time, t is time (x values), b is the slope, and a is the fictitious y-axis intercept. Algebraic conversion of this equation provided the estimated gastric emptying times at the various stages (25%, 50%, and 75%) of emptying (ie, $t_{25\%}$, $t_{50\%}$, and $t_{75\%}$, respectively) as follows:

$$t_{25\%} = -(\min[C_0;a] \bullet 0.75 - a)/b$$
$$t_{50\%} = -(\min[C_0;a] \bullet 0.50 - a)/b$$
$$t_{75\%} = -(\min[C_0;a] \bullet 0.25 - a)/b$$

where $\min[C_0;a]$ refers to the fact that in every case, the smaller of the 2 values of C_0 or a was chosen to define the start of the linear emptying phase. In more detail, that means that in instances when no lag phase was present, $C_0 = a$; however, in instances when a lag phase was present ($a > C_0$), C_0 was the starting point of linear decay.