Simultaneous Markers for Fluid and Solid Gastric Emptying: New Variations on an Old Theme: Concise Communication

Richard A. Wright, Denise Thompson, and Ibrahim Syed

University of Louisville School of Medicine and the Veterans Administration Medical Center, Louisville, Kentucky

Radiotracer techniques for the assessment of gastric emptying have become popular in the past 6 yr. A new double-nuclide technique, for the simultaneous tagging of the solid and fluid phases, is described. Technetium-99m sulfur colloid (Tc-99m SC) is used in a manner similar to that described by Meyer and colleagues, but the new technique does not involve the use of live chickens, a significant advantage over the earlier procedures. Several fluid-phase radionuclides were tested to be used in conjunction with the Tc-99m SC. Indium-111 DTPA was found to be the only compatible fluid-phase agent. This new double-tracer technique promises to be safe, economical, simple, and physiologically sound.

J Nucl Med 22: 772–776, 1981

Historically, gastric emptying rates have been difficult to standardize due to the variety of techniques used (*1–5*). Early studies used various liquid test meals and ranged from subjective assessments of the radio-opaque contrast residue in the stomach, to sophisticated techniques involving dye dilution or gamma-camera scanning of labeled fluid and fiber (*4*). The physiology of gastric emptying of liquids is primarily dependent on gastric tone (*5–7*). The tone is responsive to vagal stimuli and may be influenced by several variables, most importantly volume (*1,5–8*). The handling of solids, on the other hand, is thought to be a function of antral propulsive and retropulsive mincing action (*5,7*).

Numerous methods of measuring the emptying rates of solid food have been developed (*1–9*). These techniques have ranged from the assay of starch in a gastric aspirate after ingestion of a potato to fluoroscopic monitoring of barium-coated granules (*1–9*). Various attempts to tag protein with radionuclides and monitor gastric emptying with a gamma camera have met with disrepute because the markers dissociated from the solid phase (*8–16*). As a result, both liquid and solid emptying were being measured, without distinction between the two (*16–18*).

Meyer developed a method for determining the gastric emptying rate of solid food. He clearly demonstrated that Tc-99m SC was firmly bound in a live chicken liver (*16,17*). The Meyer technique consists of an intravenous injection of 1.0 mCi of Tc-99m SC into the wing vein of a live chicken. The Tc-99m SC is firmly incorporated into the liver. The bird is then killed and the liver is removed and diced into 1-cm cubes. It is cooked to a rubbery consistency before feeding it to a subject in a beef-stew mixture.

A double-radionuclide technique would be effective in measuring the simultaneous physiological emptying of liquids and solids without the use of a nasogastric tube. Intubation might stimulate vagal discharge and affect emptying. Several requirements are evidently necessary for a liquid-phase gastric emptying agent to be used in conjunction with the chicken liver technique. They include: (a) water solubility, (b) a tracer whose energy differs from that of Tc-99m, (c) nonadherence to chicken liver or the test meal, (d) nonabsorbability from the gastrointestinal tract, and (e) a radionuclide with energy suitable for imaging with a gamma camera. In addition, the agent selected would ideally be inexpensive and readily available. With these objectives in mind, several possible candidate radionuclides for measuring liquid-phase emptying were investigated.

Received Oct. 16, 1980; revision accepted March 26, 1981.

For reprints contact: Richard A. Wright, MD, Hall 3-E, D.D.D.N., University Hospital, 323 E. Chestnut St., Louisville, KY 40202.

METHODS

Solid-phase agent. Fresh chicken liver was purchased from a local grocery. A single, intact chicken liver was infiltrated with 1 mCi of Tc-99m SC in multiple sites using a tuberculin syringe. After the injected raw liver was rinsed with a saline solution, it was cooked to a friable consistency in a microwave oven. Five grams of cooked Tc-99m SC-labeled chicken liver were emulsified using a vortex mixer in 10 cc of pooled gastric juice (pH 3.07), obtained from five fasting subjects who had no evidence of gastrointestinal disease. Five cycles of homogenization, centrifugation, and washes with 10 cc of normal saline solution were performed over a 2-hr period. A scintillator well counter was used for analysis of the final solid and supernatant radioactivities.

Fluid-phase agents. [^{51}Cr]Na chromate, Tc-99m macroaggregated albumin, [^{131}I]rose bengal, [^{125}I]-RISA and In-111 DTPA were tested. These agents were added to the pooled gastric juice and analyzed as described above with Tc-99m SC-labeled cooked liver. The resultant solid and liquid fractions were assayed for both Tc-99m SC and each individual liquid-phase radionuclide.

[^{125}I]RISA and In-111 DTPA were further tested after adding beef stew mixed in a blender to the solid fraction. This was done in an attempt to simulate in vitro the test meal described by Meyer (*16*). Again, five cycles of centrifugation with 10 cc normal saline were carried out before analyzing the solid and liquid fractions.

The effect of pH on radionuclide stability in the fluid and solid phases was investigated for In-111 DTPA and Tc-99m SC. Pooled gastric juice (pH 3.07) was titrated to pH 1.0, 4.0, or 7.0 using either potassium hydroxide or hydrochloric acid. After emulsification with a vortex agitator the mixture was allowed to stand for 60 min. Subsequently, five cycles of centrifugation, withdrawal of supernatant, and 10 cc of normal saline washing were done with repeat emulsification and separation of the final solid and fluid fractions. These fractions were assayed separately for each nuclide.

TABLE 1.

Nuclide	Cooked liver + gastric juice	Cooked liver + normal saline
[^{51}Cr]Na chromate	F* 42%	F 51%
	S 56%	S 52%
Tc-99m MAA	F 13%	F 13%
	S 70%	S 57%
[^{131}I]rose bengal	F 2%	F 2%
	S 96%	S 73%
[^{125}I]RISA	F 81%	F 84%
	S 17%	S 13%

* F = % tracer in fluid phase, S = % tracer in solid phase.

TABLE 2. AGENT [^{125}I] RISA

	Normal saline	Gastric juice	Saliva
Cooked liver	F* 100%	F 20%	F 99%
	S 4%	S 84%	S 4%
Cooked liver + cooked potatoes	F 98%	F 16%	F 88%
	S 4%	S 88%	S 2%
Cooked liver + beef stew	F 99%	F 22%	F 95%
	S 4%	S 81%	S 7%
Cooked liver + D50	F 100%	F 35%	F 85%
	S 5%	S 66%	S 2%
Cooked liver + D5	F 94%	F 34%	F 88%
	S 4%	S 62%	S 2%

* F = % tracer recovered in fluid phase, S = % tracer recovered in solid phase, D50 = 5% dextrose.

RESULTS AND DISCUSSION

[^{51}Cr]sodium chromate and Tc-99m macroaggregated albumin were unsatisfactory for use as fluid-phase agents, since they bound significantly to the cooked chicken liver (Table 1). [^{131}I]rose bengal was eliminated because of solid phase retention. [^{125}I]RISA initially appeared to be an ideal agent, but when combined with pooled gastric juice, significant dissociation from the fluid phase occurred (Table 2). Attempts to isolate the cause of this problem showed that the gastric juice contained some factor that caused significant binding of the radionuclide with the solid fraction. Several combinations of cooked chicken liver, beef stew, and dextrose revealed that the factor was present in gastric juice but not in saliva or normal saline. Since gastric juice is an unexcludable variable in gastric emptying studies [^{125}I]RISA was unsatisfactory as a fluid-phase emptying agent to be used in combination with the combination of beef stew and Tc-99m SC-labeled chicken liver.

Technetium-99m sulfur colloid, when injected into raw chicken liver with subsequent cooking in a microwave oven to a friable consistency, remains in the solid fraction even after five cycles of emulsification, washing, and centrifugation (Table 3). It was of note that Tc-99m SC injected into previously cooked chicken liver was not retained in the solid fraction. Thus, the chicken liver must be labeled with Tc-99m SC before cooking for significant binding to occur.

Combination of solid and liquid emptying agents. Indium-111 DTPA in combination with Tc-99m SC-labeled chicken liver remained in fluid phase to a very large extent. Adjustment of the pH of the pooled gastric juice to 1.0, 4.0, and 7.0 revealed excellent separation of indium and technetium in fluid and solid phases, respec-

TABLE 3.

Agent	Saline	Cooked liver + beef stew + kool-aid Gastric juice			
		pH = 1	pH = 4	pH = 7	pH = 3.07
Tc-99m	F:* 6%	F: 8%	F: 5%	F: 11%	F: 6%
sulfur colloid	S: 94%	S: 92%	S: 95%	S: 89%	S: 94%
In-111 DTPA	F: 96%	F: 78%	F: 96%	F: 95%	F: 94%
	S: 4%	S: 22%	S: 4%	S: 5%	S: 6%
		Cooked liver + pizza + kool-aid			
		pH = 1	pH = 4	pH = 7	pH = 3.07
Tc-99m	F: 4%	F: 14%	F: 3%	F: 12%	F: 7%
sulfur colloid	S: 96%	S: 86%	S: 97%	S: 88%	S: 93%
In-111 DTPA	F: 95%	F: 79%	F: 95%	F: 96%	F: 95%
	S: 5%	S: 21%	S: 5%	S: 4%	S: 5%

* F = % tracer in fluid phase, S = % tracer in solid phase.

tively. However, at pH 1, In-111 DTPA was retained in the solid fraction to a greater extent (Table 3).

Since liquid and solid gastric emptying are apparently separate physiological functions with different determinants, a double-nuclide technique provides a better assessment of gastric emptying than previously described techniques for either solid or liquid emptying measurements. The substitution of raw chicken liver for chicken liver labeled in vivo does not significantly alter the distribution of technetium within the solid and fluid phases. While the tracer is not incorporated as homogeneously into the liver as in the Meyer method, it is firmly bound and thus provides a reliable measurement of solid emptying. Dispersion of the cooked liver in the beef stew permits the measurement of solid-phase emptying, and negates the significance of relatively nonuniform binding.

Indium-111 DTPA remains predominantly in the liquid phase throughout physiological pH ranges. Dissociation from liquid to solid phase occurs at a low pH. This poses a theoretical impediment to use of In-111 DTPA as a simultaneous fluid-phase agent in combination with Meyer's chicken liver preparation. For pratical purposes, however, the buffering action of the ingested meal and the rapid emptying of the liquid phase of the test meal (an exponential process, contrasted with linear emptying of solids) (*17,18*) preclude this phenomenon from significantly affecting gastric emptying results.

We have performed multiple gastric-emptying analyses using the described double-nuclide technique (chicken liver labeled with Tc-99m SC together with In-111 DTPA). The procedure is simple, inexpensive (less than $35.00 per study for radionuclides and test meal), and highly accurate in our experience. It does not involve the use of a live chicken, as do previously described techniques, a significant advantage in cost, space, and manpower.

If this method proves to be valid in our clinical studies and those in other centers, it may become the standard technique for the investigation of gastric stasis in patients with suspected postvagotomy syndromes and diabetic gastroparesis.

The advent of new pharmacological agents, such as metoclopramide, has heralded new prospects in the treatment of gastric emptying disorders. Definition of the type of pathophysiological defect (solid as opposed to liquid emptying) may be important in designing a dietary and/or pharmacological treatment regimen.

Dosimetry. An administered dose of 150 μCi of tagged chicken liver is sufficient to perform the study, and the local radiation to the gastrointestinal tract is not more than would be received with a single radiograph of the abdomen. A single study yields a total-body absorbed dose less than one tenth of that received during a routine chest radiograph.

One hundred microcuries of In-111 is enough to perform an analysis of liquid emptying. Indium-111 DTPA

TABLE 4. DOSIMETRY FOR ORAL ADMINISTRATION OF Tc-99m SC AND IN-111 DTPA

Organ	rads/150 μCi Tc-99m taken	rads/100 μCi In-111
Stomach wall	0.021	0.054
Small intestine	0.038	0.159
Proximal large bowel wall	0.060	0.283
Distal large bowel wall	0.057	0.649
Testes	0.00072	0.009
Ovaries	0.0137	0.122
Whole body	0.0026	0.017

is not significantly absorbed from human or canine gastrointestinal tracts (F. Hosain, personal communication). The doses listed are about the same as, or an order of magnitude less than, those received during routine nuclear medicine imaging procedures. In the present procedure, the male gonads receive 16 mrads, which is much less than the radiation dose that the average U.S. citizen receives from background radiation each year. The female gonads receive 238 mrads, which is about the same dose a person residing in Denver receives from background radiation each year.

Table 4 lists the absorbed radiation doses for the above amounts of In-111 ^{111}Indium DTPA and Tc-99m sulfur colloid. The method of calculation and the assumptions made are included in the appendix.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the expert technical assistance of Mr. Pat Higgins and the clerical expertise of Sarah L. Gibson.

APPENDIX

The average dose from a specified radionuclide can be calculated by the following simple formula (*19*):

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h S(r_k \leftarrow r_h), \quad (1)$$

where $\bar{D}$ $(r_k \leftarrow r_h)$ is the mean absorbed dose (rads) to a target organ, r_k, from a radionuclide distributed uniformly in a source organ, r_h; $\tilde{A}_h$ is the cumulated activity (μCi − h) in source organ r_h; and S is the absorbed dose per unit cumulated activity. Since there are generally several source organs, the total average dose to target organ r_k is given by:

$$\bar{D}(r_k) = \sum_h \tilde{A}_h S(r_k \leftarrow r_h). \quad (2)$$

Calculation of cumulated activity. For orally administered radiopharmaceuticals, the following equations can be used for calculating cumulated activity (*20*). For stomach

$$\tilde{A}_h = \tilde{A}_{St} = \frac{A_{St}}{\lambda s + \lambda p} \quad (3)$$

where A_{St} = activity entering the stomach (μCi), λs = biologic elimination constant for stomach (hr^{-1}), λp = physical decay constant (hr^{-1}). Average residence times for material in GI tract for standard man are shown below:

Section of GI tract	Average residence time, $\frac{1}{\lambda}$ (hr)
Stomach, S_t	1
Small intestine, SI	4
Upper large intestine, ULI	8
Lower large intestine, LLI	18

For example, the mean dose to the stomach wall, $\bar{D}_{St}$, is computed by the following expression:

$$\bar{D}_{St} = \bar{D}(St \leftarrow St) + \bar{D}(St \leftarrow SI) + \bar{D}(St \leftarrow ULI) + \bar{D}(St \leftarrow LLI) \quad (4)$$

$$= \tilde{A}_{St} S(St\ wall \leftarrow St\ contents) + \tilde{A}_{SI} S(St\ wall \leftarrow SI\ contents) + \tilde{A}_{ULI} S(St\ wall \leftarrow ULI\ contents) + \tilde{A}_{LLI} S(St\ wall \leftarrow LLI\ contents). \quad (5)$$

TABLE 5.

Section of GI Tract	Cumulated activity in μCi-hr: 150 μCi of Tc-99m oral dose	Cumulated activity in μCi-hr: 100 μCi of In-111 oral dose
Stomach (St)	134	99
Small intestine (SI)	367	380
Upper large intestine (ULI)	381	703
Lower large intestine (LLI)	279	1346

In the above:

$\tilde{A}_{SI}$ = cumulated activity in the small intestine

$$= \frac{\tilde{A}_s \lambda_s}{\lambda_{SI} + \lambda_p} \quad (6)$$

λ_{SI} = biologic elimination constant for small intestine (hr^{-1});

$\tilde{A}_{ULI}$ = cumulated activity in the upper large intestine

$$= \frac{\tilde{A}_{SI} \lambda_{SI}}{\lambda_{ULI} + \lambda_p} \quad (7)$$

λ_{ULI} = biologic elimination constant for upper large intestine (hr^{-1});

$\tilde{A}_{LLI}$ = cumulated activity in the lower large intestine

$$= \frac{\tilde{A}_{ULI} \lambda_{ULI}}{\lambda_{LLI} + \lambda_p} \quad (8)$$

λ_{LLI} = biologic elimination constant for lower large intestine (hr^{-1}).

In the above calculation the activity is assumed not absorbed into the blood. (See Table 5.)

S values could be obtained from MIRD Pamphlet No. 11 (*19*). Using the above equation, the mean doses to the small intestine, upper large intestine, lower large intestine, gonads, and whole body were estimated.

One can also calculate the cumulated activity in the different sections of the GI tract using a simple equation:

$$\tilde{A}_h = A_0\ 1.44\ Tp[1 - \exp(-0.693\ t/Tp)] \quad (9)$$

where A_0 is the administered activity in microcuries, Tp is the physical half-life of the radionuclide, t is the average residence time in the source organ, assuming no absorption into the blood.

The doses estimated using Eq. 9 result in overestimations: from 3.7% to the stomach wall, ~10% to SI, ULI, and whole body, up to 20% to LLI and gonads. This is acceptable compared with doses calculated without considering biological variability, which results in errors as much as 100-200%.

REFERENCES

1. HUNT JN, KNOX MT: Regulation of gastric emptying. In *Handbook of Physiology*. Vol. 4. Code CF, Ed. Washington, DC, American Physiology Society, 1968, pp 1917-1935
2. GEORGE JD: New clinical method for measuring the rate of gastric emptying: the double sampling test meal. *Gut* 9: 237-242, 1968
3. BROMSTER D, CARLBERGER G, LUNDH G: Measurement

of gastric emptying rate using ^{131}I-HS A. A methodological study in man. *Scand J Gastroenterol* 3: 641-653, 1968

4. STADAAS J, AUNE S: Intragastric pressure/volume relationship before and after vagotomy. *Acta Chir Scand* 136: 611-615, 1970
5. MEYER JH, MANDIOLA S, SHADCHEHR A, et al: Dispersion of solid food by the canine stomach. *Gastroenterology* 72: A-79/1102, 1977 (abst)
6. BUCKLER KG: Effects of gastric surgery upon gastric emptying in cases of peptic ulceration. *Gut* 8: 137-147, 1967
7. COLMER MR, OWEN GM, SHIELDS R: Pattern of gastric emptying after vagotomy and pyloroplasty. *Br Med J* 2: 448-450, 1973
8. HANCOCK BD, BOWEN-JONES E, DIXON R, et al: The effect of metoclopramide on gastric emptying of solid meals. *Gut* 15: 462-467, 1972
9. HARVEY RF, MACKIE DB, BROWN NJG, et al: Measurement of gastric emptying time with a gamma camera. *Lancet* 1: 16-18, 1970
10. GRIFFITH GH, OWEN GM, CAMPBELL H, et al: Gastric emptying in Health and in gastroduodenal disease. *Gastroenterology* 54: 1-7, 1968
11. VAN DAM APM: The gamma camera in clinical evaluation of gastric emptying. *Radiology* 110: 155-157, 1974
12. HEADING RC, TOTHILL P, LAIDLAW AJ, et al: An evaluation of ^{113m}indium DTPA chelate in the measurement of gastric emptying by scintiscanning. *Gut* 12: 611-615, 1971
13. DOZOIS RR, KELLY KA, CODE CF: Effect of distal antrectomy on gastric emptying of liquids and solids. *Gastroenterology* 61: 675-681, 1971
14. MEYER JH, MACGREGOR IL, GUELLER R, et al: ^{99m}Tc-tagged chicken liver as a marker of solid food in the human stomach. *Am J Dig Dis* 21: 296-304, 1976
15. MACGREGOR IL, MARTIN P, MEYER JH: Gastric emptying of solid food in normal man and after subtotal gastrectomy and truncal vagotomy with pyloroplasty. *Gastroenterology* 72: 206-211, 1977
16. MALAGELADA J-R: Physiologic Basis and clinical significance of gastric emptying disorders. *Dig Dis Sci* 24: 657-661, 1979
17. REES WD, GO VLW, MALAGELADA J-R: Antroduodenal motor response to liquid-solid and homogenized meals. *Gastroenterology* 76: 1438-1442, 1979
18. MALAGELADA J-R, GO VLW, SUMMERSKILL WHJ: Different gastric, pancreatic, and biliary responses to solid-liquid or homogenized meals. *Dig Dis Sci* 24: 101-110, 1979
19. SNYDER WS, FORD MR, WARNER GG, et al: Absorbed dose per unit cumulated activity for selected radionuclides and organs. MIRD Pamphlet No. 11, New York, Society for Nuclear Medicine, 1975, pp 5-257
20. COFFEY JL, WATSON EE: The influence of effective residence time on the radiation dose to the gastrointestinal tract. In *Radiopharmaceutical Dosimetry*. HEW Publication 76-8044, 1976, pp 230-238

COMPUTER COUNCIL
AND
INSTRUMENTATION COUNCIL MEETING
DIGITAL MEDICAL IMAGING IN THE FUTURE

January 28-29, 1982 **Phoenix, Arizona**

The Computer and Instrumentation Councils of the Society of Nuclear Medicine will meet January 28 and 29, 1982, in Phoenix, Arizona.

A topical symposium on Digital Medical Imaging in the Future is being sponsored by the Councils. It will consist of invited presentations, contributed papers, and active attendee discussion. The main emphasis will be on advances and new horizons in hardware and computer applications, such as microprocessors, controlled cameras, array processors, networking, mass storage devices, displays, and interactive languages. There will be only one session presented at a time. The abstracts of the meeting will be available prior to the meeting. The proceedings of the meeting will be published.

The Councils welcome proferred papers in all of the above categories, but papers on other aspects of computer and other instrumentation sciences are also acceptable. Abstracts of 300 words should contain a statement of purpose, the methods used, results, and conclusions, as well as the title, and author's name and full address. Abstracts may be accompanied by supporting data.

Original abstracts and supporting data should be sent in triplicate to:

Barbara Y. Croft, Ph.D.
Department of Radiology, Box 170
University of Virginia
Charlottesville, VA 22908
Tel: (804)924-5201

ABSTRACTS MUST BE RECEIVED BY OCTOBER 1, 1981.