planar study. However, collecting three views is routine in planar studies. In our laboratory, we typically collect three rest planar studies in approximately the time required for our resting SPECT acquisitions (about 30–35 min).

CONCLUSION

Global EF can be easily measured from reprojected SPECT GBP images using a counts-based method. This technique yields background activity levels that are so low that background correction is probably not necessary. In addition, it seems that global EF is not measurably affected by the attenuation inherent in SPECT imaging. Finally, rSPECT EFs were greater than planar EFs by a factor of 1.4, and our results suggest that the SPECT EFs may be more accurate than those from planar images. The discrepancy arises because the angle of view of planar images is sufficiently far from the long-axis to cause a significant drop in the measured EF, due to atrial overlap. The exact amount by which the EF is decreased will vary from patient to patient. rSPECT avoids this problem since images can always be presented in the true long-axis view.

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Reappraisal of Quantitative Esophageal Scintigraphy by Optimizing Results with ROC Analyses

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This study investigates whether systematic analyses of methodological issues contribute to improve and renew the diagnostic role of quantitate esophageal scintigraphy. **Methods:** Forty-seven patients with normal (n = 26) and pathologic (n = 21) esophageal function were studied with scintigraphy and manometry, using the latter findings as the gold standard. Scintigraphic data were analyzed by receiver operator characteristic (ROC) methods to: establish the optimal decision threshold for six different quantitative parameters, evaluate their inherent discrimination capacity and compare liquid compared with solid bolus data. **Results:** Quantitative parameters have shown remarkable differences in their potential to discriminate between normal and pathologic findings (percentage of emptying at definite time points > mean time > transit time > mean transit time > T_{max}). Sensitivity of 95% at a specificity of 96% was the optimum obtained. At comparable specificity levels, solid bolus studies generally demonstrated higher sensitivity than liquid bolus studies. **Conclusion:** The diagnostic performance of optimized esophageal scintigraphy is close to that of manometry. Our findings do not only renew the role of esophageal scintigraphy as an accurate screening test for esophageal motility disorders but also invalidate recent reservations about the diagnostic potential of this method.

Key Words: esophageal scintigraphy; quantification; ROC analyses

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In 1972, Kazem (*1*) reported on the use of various radiopharmaceuticals and a gamma camera to monitor swallowing. Since then, several investigators have established scintigraphic techniques for the evaluation of esophageal motility disorders (*2–10*). Although several drawbacks from previous methods have been solved by recent developments [i.e., condensed images for a more accurate depiction of esophageal events (*5,7,8,11–14*) or multiple swallow protocols to compensate for the intraindividual variation between repetitive swallows (*10,15*)], the diagnostic role of esophageal scintigraphy is still under discussion.

In earlier reports, several authors proposed that radionuclide transit studies are a sensitive screening test to detect esophageal motility disorders (*3,6,16*). Others concluded that esophageal scintigraphy is of limited use only (*17,18*), and some investigators even stated that this approach has almost no diagnostic significance (*19,20*).

There are several reasons that may account for the discrepant appraisal of esophageal scintigraphy, such as the obvious differences in the methodological approach. In this context, little attention focused on relevant issues such as: the kind of quantitative parameters used, how decision thresholds for discriminating normal compared with pathologic function were established, whether studies were performed with liquid or solid boluses or whether single compared with multiple-swallow protocols were applied to establish scintigraphic results.

The aim of this study was to determine whether or not further

TABLE 1
Clinical Diagnoses and Classification Manometric Results

Clinical diagnosis	N	Manometry	
		Normal	Pathologic
Connective tissue disease	13	9	4
Achalasia	7	0	7
Reflux/esophagitis	7	7*	0
Diffuse esophageal spasm	4	1	3
Diabetes mellitus	3	1	2
Other	13	8	5
Total	47	26	21

*Normal with respect to the contractions of the tubular esophagus but not with respect to lower esophageal sphincter function.

systematic analyses of the factors addressed may contribute to optimizing the results of quantitative esophageal scintigraphy. For this purpose, several parameters previously applied to quantitate esophageal function were analyzed with receiver operator characteristic (ROC) methods (*21,22*) such as: (a) establish the optimal decision threshold for each parameter, (b) evaluate their inherent discrimination capacity, (c) compare liquid compared with solid bolus data and (d) appraise the results evaluated.

MATERIALS AND METHODS

Patients

Forty-seven consecutive patients (21 men, 26 women, age range 33–72 yr) were referred to the departments of nuclear medicine and internal medicine for investigation of esophageal function and studied with scintigraphy and manometry. The patients suffered from suspected or manifest diseases, commonly associated with esophageal motor dysfunction such as connective tissue disease (i.e, progressive systemic sclerosis, mixed connective tissue disease, dermatomyositis), achalasia, esophageal spasm, gastroesophageal reflux disease, diabetes mellitus and other disorders as noncardiac chest pain, myasthenia gravis and unexplained dysphagia. The clinical diagnoses of the patients and classification of their manometric results are summarized in Table 1.

Esophageal Scintigraphy

Acquisition and processing protocols for evaluation of multiple consecutive swallows were previously described in detail (*10,14*).

Acquisition. Patients were studied in the supine position with a LFOV gamma camera in the posterior position. The gamma camera was connected to a commercially available computer system . Esophageal transit studies were performed with six radiolabeled liquid and semisolid test boluses. The transit of liquid bolus was studied with water (10 ml per swallow, labeled with approximately 10 MBq ^{99m}Tc-sulfur colloid each). Solid bolus investigations were performed with a baby paste prepared according to a standardized protocol: 20 g instant Alete Milch-Fertigbrei® were dissolved in 40 ml water and administered in portions of 10 g per swallow, labeled with approximately 5 MBq ^{99m}Tc-sulfur colloid each. Compared to the consistency of, for example, a compact gelatine bolus or cubes of chicken liver, the administered baby paste is more semisolid in texture. Its viscosity was adjusted so that it did not drop from the spoon. Normally, a marked dispersion of the bolus during its esophageal passage was not observed.

During dynamic data acquisition (240 frames, 0.8 sec/frame, byte mode, 64 × 64 matrix), a radiolabeled test bolus was administered every 30 sec. The patient was asked to ingest the bolus by one single deglutition and then to avoid swallowing for 30 sec until the next bolus was offered.

Image Processing. From each dynamic study, a condensed image was created, showing the six consecutive swallows in a space-time matrix. The method and algorithms used for image condensation were described previously (*11,13*). The condensation procedure was confined to a user-defined region of interest which comprised the esophagus from the pharynx to the lower sphincter. In the raw version of a condensed multiple-swallow image, single swallows were standardized with respect to their starting points, arranged consecutively and added to a condensed sum image.

For quantitative evaluation, time-activity curves were derived from the sum image. Curves were generated by plotting the counting rates of the columns assembled in each image. The counting rate of each column was obtained adding its single-pixel data. Three-point smoothing was performed with all curves. The time-activity curves were used to calculate the following quantitative parameters:

1. T_{max} = time from the starting point of a swallow until the maximal counting rate was reached (*9*).
2. Transit time = time from the starting point of a swallow until activity fell to 10% or less of the peak activity (i.e., 90% emptying time) (*6*).
3. Mean transit time: $\frac{\Sigma cts(t)}{cts_{max}}$ (*9*).
4. Mean time: $\frac{\Sigma cts(t) \times t}{\Sigma cts(t)}$ (*9*).

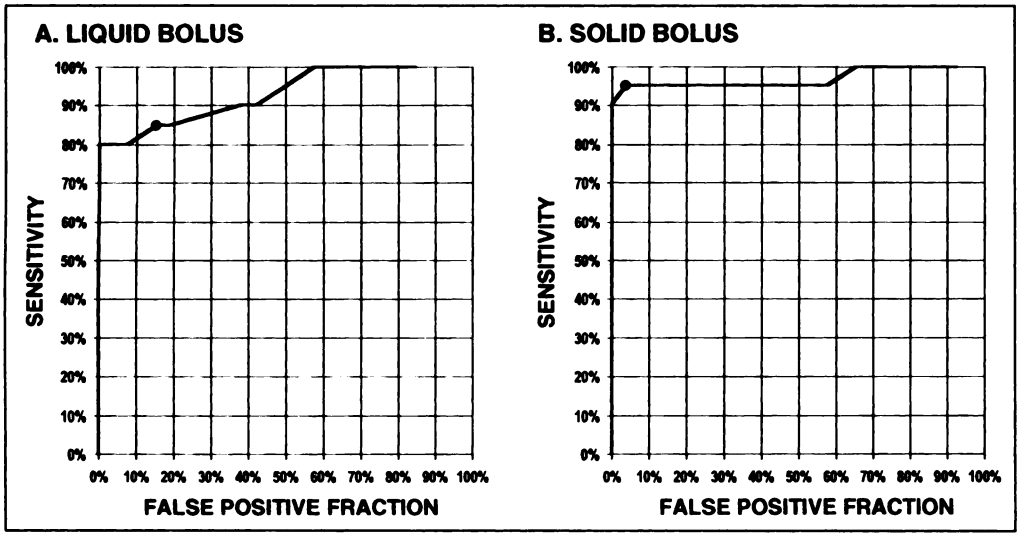

FIGURE 1. Results for the parameter esophageal emptying$_{12sec}$. Liquid (A) and solid (B) bolus studies. Filled circle is optimum inherent discrimination capacity of a tested diagnostic system.

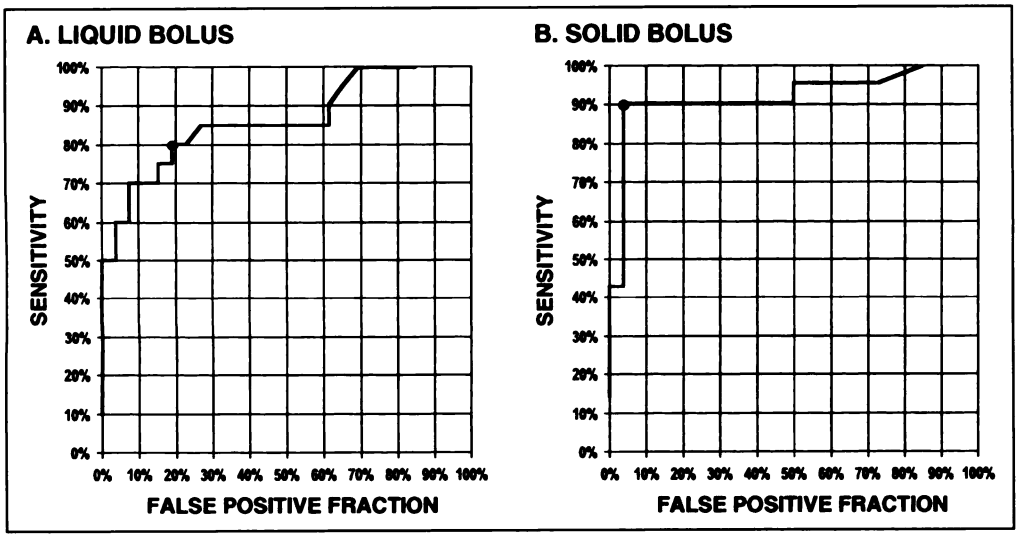

FIGURE 2. Results for the parameter esophageal emptying$_{Tmax.+10sec.}$. (A) Liquid and (B) solid bolus studies. Filled circle is optimum inherent discrimination capacity of a tested diagnostic system.

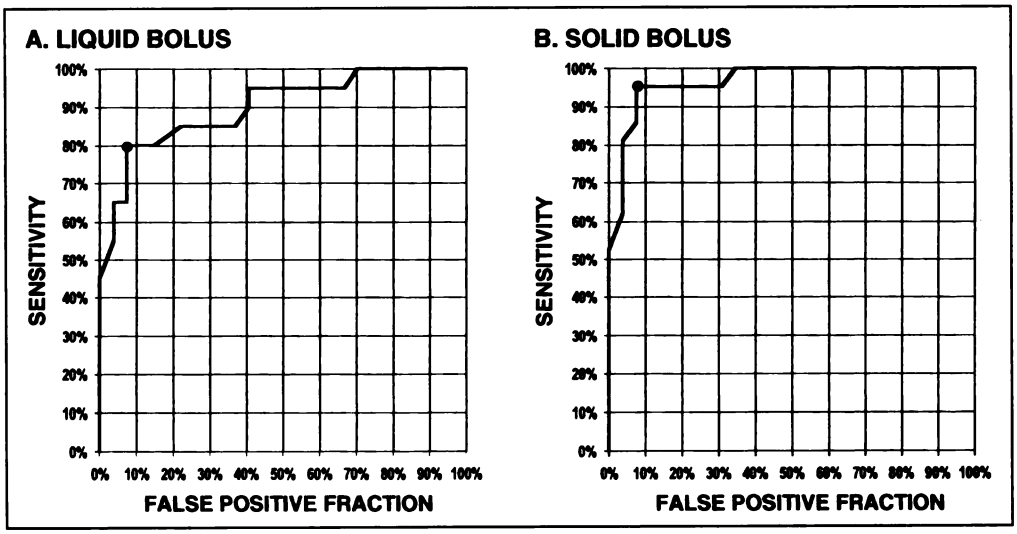

FIGURE 3. Results for the parameter mean time. (A) Liquid and (B) solid bolus studies. Filled circle is optimum inherent discrimination capacity of a tested diagnostic system.

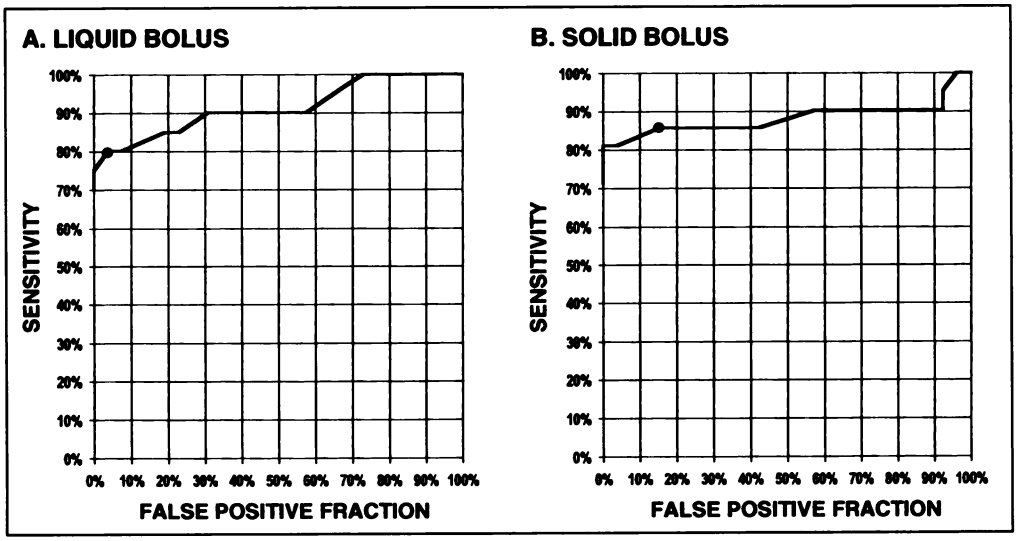

FIGURE 4. Results for the parameter transit time. (A) Liquid and (B) solid bolus studies. Filled circle is optimum inherent discrimination capacity of a tested diagnostic system.

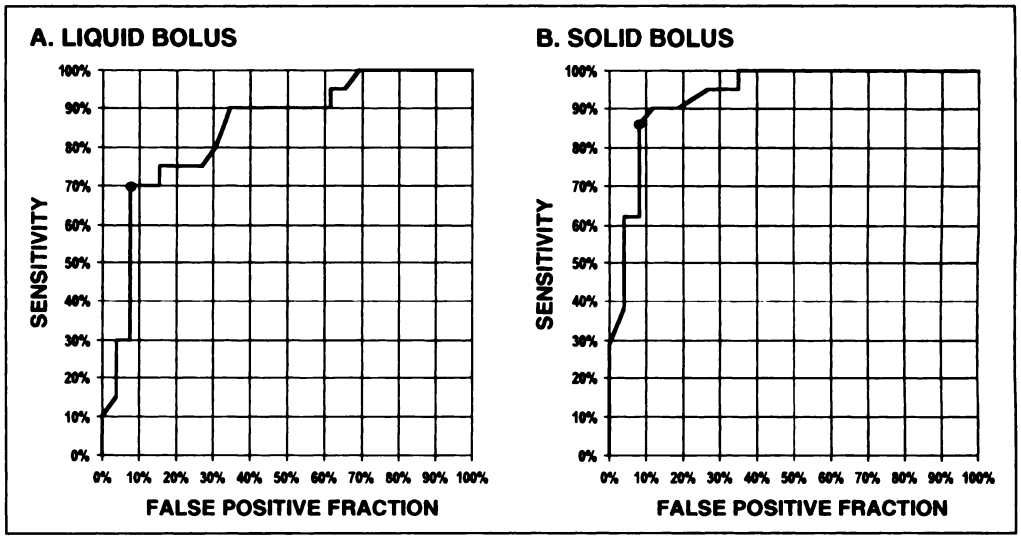

FIGURE 5. Mean transit time results. (A) Liquid and (B) solid bolus studies. Filled circle is optimum inherent discrimination capacity of a tested diagnostic system.

5. Esophageal emptying$_{Tmax+10sec}$: emptying in percent of the peak activity 10 sec after T_{max} (*10*).
6. Esophageal emptying$_{12sec}$: emptying in percent of the peak activity 12 sec after the swallow was initiated (*14*).

Given that the esophagus may not be completely cleared from residual activity between consecutive single swallows in some disorders or normal variants of swallowing, background (i.e., residual activity) correction was performed as outlined previously (*10*). This approach explains that, for single swallows particularly, emptying may exceed the value of 100%, for example, if residual activity from a preceding swallow will be cleared with the following one. This phenomenon can infrequently result in emptying values slightly exceeding 100% in sum images in patients with variants of normal function, which may be considered an artifact of background subtraction. Since this potential methodological drawback has no effect on the correct classification of scintigraphic data as normal, so far no attempt was made to compensate for it.

In a strict sense, the parameters mean transit time and mean time used in this study reflect a more modified than a true mean transit time and mean time since the curves did not all drop to zero values. This should be kept in mind for correct interpretation of the findings obtained for those parameters.

As previously outlined, in the sum images of normal function, counting rates of maximal 800-1200 cts/frame (=column) and minimal 80–180 cts/frame were observed (*10*). In patients with delayed emptying, the counting rates per frame were higher compared to normals and showed a considerable variation in dependence of the severity of the underlying disorder (maximal 4000 cts/frame and minimal 2500 cts/frame).

Esophageal Manometry

Manometry was performed with a seven-lumen tube of 5.0 mm external diameter. Each lumen of the catheter assembly had a side hole of 1.0 mm diameter and was continously perfused with water at 1.0 ml/min by a low compliance pneumohydraulic pump. Pressure rise with total occlusion of a side hole was >250 mmHg/sec. The sonde was inserted with the openings placed 0.5, 1, 4, 9, 14, 18 and 22 cm above the lower esophageal sphincter. Esophageal intraluminal pressure was transmitted to a pressure transducer and displayed on a chart recorder. .

Manometric findings were interpreted according to visual and quantitative criteria as outlined by Richter et al. (*23*). The mean value of esophageal contraction amplitudes and progression of the peristaltic waves were used as the criteria for defining normal tubular esophageal function as compared to abnormal. In the present investigation, mean values of peristaltic amplitudes < 30 mmHg were prospectively defined as pathologic (*23*). Since patients presenting with simultaneous contractions exclusively had pressure amplitudes <30 mmHg, they were not evaluated as a separate group. According to these criteria, the sensitivity and specificity of scintigraphic findings were calculated.

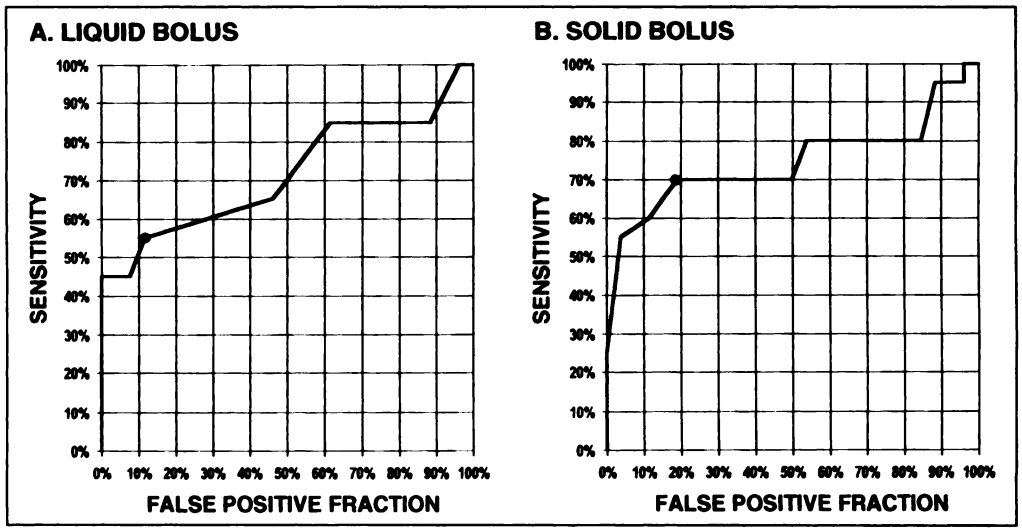

FIGURE 6. Results for T_{max}. (A) Liquid and (B) solid bolus studies. Filled circle is optimum inherent discrimination capacity of a tested diagnostic system.

TABLE 2
Decision Threshold at which Best Discrimination between Normal and Pathologic Function Was Observed for Each Quantitative Parameter

Parameter	Liquid bolus	Solid bolus
Esophageal emptying$_{12\ sec}$	91%	85%
Esophageal emptying$_{Tmax\ +\ 10\ sec}$	88%	86%
Mean time	6.2 sec	6.4 sec
Transit time	12.1 sec	12.1 sec
Mean transit time	8.3 sec	8.4 sec
T_{max}	2.1 sec	3.7 sec

ROC Analyses

Quantitative data of esophageal function were categorized in true- and false-positive and true- and false-negative findings using the results of esophageal manometry as the gold standard. As shown in Table 1, the evaluation of sensitivity and specificity was based on a comparable number of patients (n = 21 and n = 26, respectively). Positive and negative manometric recordings were present in almost all investigated categories of esophageal disease.

Sensitivity and specificity are meaningful terms to describe the performance of a diagnostic imaging system. This pair of indices, however, does not provide a unique description of diagnostic efficacy because their values depend on the arbitrary selection of a decision threshold. By variation of the threshold (emptying parameters: range 0%-100%; time parameters: range 0 sec to the maximum value observed), multiple pairs of sensitivity and specificity are provided. These pairs can be plotted as ROC curve which is used to define the optimal threshold for decision making and describe the inherent discrimination capacity of the diagnostic system.

In the present study, the scintigraphic data of liquid and solid bolus studies were categorized for each quantitative parameter. Results were plotted as ROC curves. For each parameter, the total area under the curve was calculated as well as the area under that part of the curve which corresponds to false-positive rates between 0% and 20%.

RESULTS

Figures 1–6 show the ROC curves for the quantitative parameters investigated. The A panels show data for the liquid bolus investigations, B panels show the solid bolus studies. The decision threshold at which the best discrimination between normal and pathologic function was observed is indicated in each graph, the respective threshold values are listed in Table 2. The two best sensitivity/specificity pairs obtained for each parameter are summarized in Table 3.

TABLE 3
Diagnostic Performance of Esophageal Scintigraphy: Comparison of the Two Best SN/SP Pairs of Various Quantitative Parameters Established for Liquid and Solid Bolus Studies Using a Multiple-Swallow Protocol

	Liquid bolus		Solid bolus	
Parameter	SN/SP	SN/SP	SN/SP	SN/SP
Esoph. emptying$_{12\ sec}$	85/85	80/100	95/96	90/100
Esoph. emptying$_{Tmax\ +\ 10\ sec}$	80/81	75/85	95/50	90/96
Mean time	85/78	80/92	95/92	81/96
Transit time	85/81	80/96	86/85	81/96
Mean transit time	75/85	70/92	88/90	86/92
T_{max}	65/54	55/88	70/81	60/88

SN = sensitivity (%); SP = specificity (%), Esoph. = esophageal

TABLE 4
Diagnostic Performance of Esophageal Scintigraphy: Comparison of Inherent Discrimination Capacity of Various Quantitative Parameters by Evaluation of Total and Fractional Areas Under the ROC Curves

	Area under the ROC curve (%)			
	Total		False-positive fraction from 0%–20%	
Parameter	Liquid	Solid	Liquid	Solid
Esophageal emptying$_{12\ sec}$	93	97	83	96
Esophageal emptying$_{Tmax\ +\ 10\ sec}$	86	92	63	82
Mean time	90	97	72	87
Transit time	91	88	82	84
Mean transit time	84	94	53	75
T_{max}	72	75	49	58

The quantitative parameters have shown remarkable differences with respect to their potential to discriminate between normal and pathologic findings. As indicated by the areas under the ROC curve (Table 4), the best discrimination capacity was observed for the parameter esophageal emptying$_{12sec}$ followed by mean time, esophageal emptying$_{Tmax+10sec}$ and transit time. Results for mean transit time were less satisfying. The worst performance was observed for the parameter T_{max}. The differences between the single parameters became more evident particularly if the area under the curve corresponded to false-positive rates between 0% and 20% (Table 4).

In general, the performance of solid bolus studies was better compared to those of liquid ones. At comparable specificity levels, solid bolus studies demonstrated a higher sensitivity than liquid bolus studies. A combined evaluation of two or more parameters did not further enhance the discrimination capacity observed for the best single parameter.

DISCUSSION

Radionuclide studies of esophageal transit are accepted as an easy, readily available and noninvasive test for the assessment of esophageal motility disorders (*3,6,7,9,10,13,16*). Its diagnostic significance, however, is still controversial. Table 5 summarizes relevant reports in the literature addressing this issue in the last decade. The authors cited have found that radionuclide transit studies may detect esophageal dysfunction with sensitivities ranging from 44% to 100% and specificities ranging from 47% to 89%. The reasons for those heterogenous observations have not been systematically elucidated yet. In addition to other aspects (e.g., composition of the patient population), it may be assumed that differences in the applied methodology substantially account for the reported disagreement. Selection of quantitative parameters, definition of decision thresholds,

TABLE 5
Reports in the Literature on Sensitivity and Specificity of Radionuclide Transit Studies for Evaluation of Esophageal Dysfunction

Authors	Yr	Sensitivity	Specificity
Russell et al. (*3*)	1981	100%	62%
Blackwell et al. (*6*)	1983	84%	84%
De Caestecker et al. (*17*)	1986	64%	77%
Mughal et al. (*19*)	1986	44%	71%
Eriksen et al. (*24*)	1987	84%	54%
Gilchrist et al. (*20*)	1987	67%	47%
Holloway et al. (*18*)	1989	70%	89%
Taillefer et al. (*16*)	1990	92%	88%

bolus consistency and use of single compared with multiple-swallow protocols have to be discussed in this context and are addressed by the current investigation.

Since ROC analysis is a powerful tool to describe the performance of diagnostic imaging systems (*21,22*), we applied this methodology to six established parameters with the aim of optimizing quantitative evaluation of esophageal function.

Our data indicate that the potential to discriminate normal from pathologic function may substantially depend on the quantitative parameter used. The optimum in our study was obtained using esophageal emptying$_{12sec}$ as parameter which provided a sensitivity of 95% and a specificity of 96% compared to manometry. For the parameters esophageal emptying$_{Tmax.+10sec}$, mean time, transit time and mean transit time at a similar specificity sensitivity was somewhat lower. T_{max} presented the lowest discrimination capacity of all tested parameters.

Generally, parameters reflecting the percentage of emptying at particular time points seemed to be advantageous over time parameters. Pathophysiological explanations for this observations remain to be established. One might speculate that parameters based on the slope of time-activity curves allow a better separation between normal and pathologic function than those which depend on the area under the curve.

In concordance with our findings, Ham et al. (*9*) previously showed sensitivity for detecting esophageal dysfunction may depend on the parameter used for quantitation. In their report, however, scintigraphic data were not compared with a reference method.

In our study, for each quantitative parametric, decision thresholds were varied to define the respective optimum for decision making. Those thresholds providing high values for both sensitivity and specificity were considered best since our aim was to establish a diagnostic system which permits both to reliably detect and also exclude esophageal dysfunction. In contrast to our study, optimizing decision thresholds was not a major issue in previous reports (Table 5). Since sensitivity and specificity vary inversely as the decision threshold is changed (*21*), the remarkable difference in respective data pairs observed in some studies (*3,19,24*) may indicate that decision criteria were defined too strictly [resulting in high specificity combined with low sensitivity (*19*)] or vice versa [high sensitivity combined with low specificity (*3,24*)].

With few exceptions (*24*), esophageal transit studies have been predominantly performed with liquid rather than solid test boluses. We used an intrasubject comparison of liquid compared with solid bolus data and showed that bolus consistency may significantly influence results. An increase in sensitivity, at comparable levels of specificity, suggests a preference for solid over liquid boluses. From a pathophysiological point of view, one possible explanation for this observation may be that the pharyngeal ejection force propels the leading edge of liquid boluses immediately to the gastroesophageal junction, leaving only minor work to be done by peristalsis. In contrast, more viscous boluses are only propelled over the proximal half of the esophagus, thereby requiring more intense peristaltic action to complete transport over the distal half (*25*). This difference may account for a more sensitive detection of functional impairment with solid boluses compared to liquid ones.

Advantages and necessity of multiple-swallow protocols have been previously discussed by several investigators (*10,13,15*). The authors cited in Table 5 based the evaluation of esophageal function on the analysis of one or two single swallows. Due to the high intraindividual variation between single swallows (*10–12,15,26,27*), there is a high chance for false-positive or negative results applying this approach. Some investigators critically analyzing their results have recognized this particular drawback and demanded multiple swallow investigations (*18,20*). In the current study, an established multiple-swallow protocol (*10,14*) was used to assess esophageal function. As demonstrated earlier, esophageal motility disorders are more accurately characterized by this approach than by single swallow investigations (*10*).

The spectrum of diseases investigated may be another factor contributing to the different appraisals of esophageal transit studies. There were major differences in the cited reports (Table 5) with respect to the composition of the patient population. In comparing the results of different reports, it is of importance, whether more severe or mild disorders have been predominantely studied. In the present investigation, the composition of the patient population may be considered balanced. First, the number of patients with normal (n = 26) and pathologic findings (n = 21) used for the evaluation of sensitivity and specificity was comparable. Second, a variety of different diseases was investigated. Due to this heterogeneity, our data may be less biased than that of other reports that do not account for this specific aspect.

One drawback of the current study may be the relatively low number of patients investigated. Larger groups of patients in each of a number of defined diagnostic categories may be advantageous, but this could be the basis of future research to validate the diagnostic thresholds determined from the present investigation.

CONCLUSION

Optimized esophageal scintigraphy (e.g., multiple-swallow test protocol, solid bolus studies, use of adequate quantitative parameters and decision thresholds) may discriminate between normal and pathologic function with a sensitivity (95%) and a specificity (96%) close to the one of the gold standard. Thus, our results may not only renew the role of esophageal scintigraphy as an accurate diagnostic test for the detection and exclusion of esophageal motility disorders but also invalidate recent reservations concerning the diagnostic potential of this method.

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Feasibility of Estimating Glomerular Filtration Rate in Children Using Single-Sample Adult Technique

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This work was undertaken to verify whether a single-sample adult technique, when applied using body surface-corrected plasma concentration, can be used in place of specific pediatric method to estimate ^{51}Cr-EDTA renal clearance in children. **Methods:** In a series of 90 children (aged 0.1 to 15 yr), ^{51}Cr-EDTA renal clearance was calculated using four different approaches. The first approach used specific pediatric single-sample methods; three techniques were chosen and they all used 120-min plasma concentration. The second approach used the same three specific pediatric methods, but they were applied using 120-min plasma concentration prescaled for 1.73 m^2 body surface area. The third approach used single-sample methods designed for adults; three methods were again chosen. They all used 240-min plasma concentration. The fourth approach used the same adults algorithms, but they were applied using 240-min plasma concentration prescaled for 1.73 m^2 body surface area. **Results:** Clearances calculated using the three specific pediatric methods were all closely cross-correlated regardless of whether or not the plasma concentration was prescaled. The use of classical adult methods produced in some cases obviously erroneous clearance values. Improvements were observed when the same adult methods were applied using prescaled plasma concentration. Nonetheless, the clearance values obtained only fairly correlated with those obtained using specific pediatric methods. **Conclusion:** The single-sample adult technique using plasma concentration prescaled for 1.73 m^2 body surface area cannot be used in place of a specific pediatric single-sample method to estimate ^{51}Cr-EDTA renal clearance in children.

Key Words: glomerular filtration rate; single-blood sample method; pediatrics

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The single-sample method is now widely used for estimating renal clearance. Depending on the tracer used, equations have been determined which allow the conversion of a distribution volume at a predetermined time into an estimate of renal clearance (*1–9*). Specific pediatric equations also have been developed (*10–13*). While all these methods give satisfactory results, the requirement of using different methods when dealing with adults or children has motivated the search for an age- independent technique (*14–16*). Within this scope, the approach of Bubeck et al. (*15,16*) was very attractive, especially because of its simplicity. They used ^{99m}Tc-MAG3 (*15,16*) to show that adult formulas can be used in children by scaling down the plasma concentration for body surface areas. They claimed that this principle was applicable for any radiotracer even if, unless we are mistaken, no validation for a glomerular agent has been reported so far.

This work was undertaken to verify whether the single-sample adult technique using plasma concentration prescaled for 1.73 m^2 body surface area could be used in place of a specific pediatric single-sample method to estimate ^{51}Cr-EDTA renal clearance in children.

MATERIALS AND METHODS

Patients

Ninety patients were selected from our single injection (two blood samples) ^{51}Cr-EDTA database (*12*) based on the following criteria: the patient was less than 15 yr old; the first blood sample was taken between 110 and 120 min after intravenous injection of the tracer; and the second blood sample was obtained between 235 and 240 min after tracer administration.

Estimates of Chromium-51-EDTA Clearance

Chromium-51-EDTA renal clearance was estimated using four different approaches. The first used specific pediatric single-sample methods. Three techniques were chosen: (a) Groth and Aasted method (*10*), (b) Tauxe et al. formula (*11*), and (c) Ham and Piepsz converting equation (*12*). All three of these methods used the 120-min plasma concentration. Detailed descriptions of these algorithms are presented in the Appendix. The second approach used the same three specific pediatric methods, but they were applied using the 120-min plasma concentration prescaled for 1.73 m^2 body surface area. The third approach used single-sample methods designed for adults. Three methods were chosen: (a) Morgan et al. converting equation (*2*), (b) Tauxe et al. formula (*3*), and (c) Christensen and Groth method (*5*). These three methods used the 240-min plasma concentration. Detailed descriptions of

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