Esophageal Scintigraphy: Reproducibility and Normal Ranges

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Esophageal scintigraphy has been rather widely used, but much debated as a simple screening method of esophageal dysfunction. However, reports of normal ranges, age dependence and reproducibility are very limited. We studied 60 healthy subjects with a mean age of 43 yr (26, 19, 15 subjects aged 20–39, 40–59, and 60–79 yr) to establish normal ranges and variations of esophageal mean transit time and residual activity measured by a radionuclide method using [^{99m}Tc] pertechnetate labeled water. Mean transit time was calculated by Zierler's formula. The median values and 95% percentiles of single measurements of MTT and residual activity in the supine position were 6.1 (3.2–11.5) sec and 11.5 (3.0–50)%, respectively. The coefficients of variation (CV) were 20%–35% for mean transit time and 85%–120% for residual activity in the sitting and supine positions. When double measurements were used, the CVs were reduced to 10% for MTT and 40% for residual activity in the supine position. The values did not change with age except for a higher frequency of spikes in subjects over 40 yr. The study has demonstrated that mean transit time for radiolabeled water in the esophagus of healthy subjects, measured by double determinations, has rather low, age-independent, interobserver and intersubject variabilities. In contrast, measurements of residual activity shows unacceptably high variations.

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Esophageal scintigraphy is a method which evaluates the transport of radiolabeled fluids or semi-solid substances through the esophagus. In 1972, Kazem (*1*) introduced radionuclide esophageal transit, and later it has been described in several studies using many different approaches (*2–6*). This paper presents an evaluation of our method in normal subjects focusing on mean transit time (MTT) calculations of a single swallow ^{99m}Tc fluid technique. Previous studies (*2–6*) have employed methods with repeated swallows but the investigations have been hampered by a limited number of subjects investigated. The use of ^{81m}Kr as an ideal isotope for the study of esophageal transit using a single swallow technique with the centroid formula calculation of MTT has been proposed (*7*). The single swallow technique was also used in a study where scintigraphy was compared with esophageal manometry (*8*). Recently, O'Connor et al. have used a single swallow method with semisolids (*9*) and a condensed image technique, as previously described (*10, 11*).

Esophageal scintigraphy has been used in many clinical investigations showing a prolonged esophageal transit e.g. in patients with achalasia (*2,4,5,9,12,13*) and systemic sclerosis (*2,9,17,18*). It has been claimed that radionuclide esophageal transit determinations were of limited value for screening patients with dysphagia (*8*), but several other papers have advocated the use of this method (*3,5,16,20*). We and others have used the method for evaluation of patients with goiter (*14,15*), enlarged left atrium (*15*), diabetic autonomous neuropathy (*17,21*), angina-like chest pain (*19*), and in gastroesophageal reflux (*2,9,13*).

The method is easy to perform, noninvasive, non-traumatic to the patient and easy to handle for the investigator. The examination lasts for about 15 min and the calculations can be done semi-automatically on a computer. The examination is quantitative and causes less radiation compared to cineradiography (*15*).

The aim of the present study was to establish a normal range, and to describe the inter- and intra-observer variation and the inter- and intra-individual variation of mean transit time measurements in healthy adults between 20 and 79 yr.

METHODS AND SUBJECTS

The study comprised 60 healthy volunteers, 29 women with a mean age of 47 yr (range 20–79 yr) and 31 men with a mean age of 40 yr (range 21–76 yr). The subjects were divided into three groups: 20–39 yr of age (10 women and 16 men); 40–59 yr of age (10 women and 9 men); and 60–79 yr of age (9 women and 6 men). The volunteers were all without gastrointestinal symptoms and took no medicine. None of the volunteers were overweight. Alcoholism, drug addiction and prior gastrointestinal surgery excluded participation in the study. The healthy volunteers were hospital staff, students or elderly pensioners who gave informed consent in accordance with the Helsinki II declaration. The study was approved by the local ethical committee.

Esophagus Scintigraphy

All subjects were investigated in the supine position. The volunteers were reexamined after 3–7 days. Eleven subjects were

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examined with only one swallow in the supine position, 49 subjects made two separate swallows both in the supine and in the sitting positions. In 46 subjects, the passage of capsules was also investigated.

Esophageal transit was determined using a GE-Maxi gamma-camera with a low-energy, general-purpose parallel-hole collimator and a Digital PDP-11 computer. The patients swallowed the bolus on command. They trained by swallowing pure water and then swallowed boluses of 15 ml of water labeled with 5 MBq [^{99}Tc]pertechnetate. The swallows were repeated within 1–2 min, and the subjects were instructed to avoid multiple swallows and the volunteers practiced swallowing before the investigation started. Emotional disturbances were avoided, and the subjects were carefully informed to avoid unnecessary anxiety. An anterior projection was used. A radioactive marker was placed over the cricoid cartilage to mark the level of the upper esophageal sphincter. The bolus passage was followed on a monitor. The data acquisition was interrupted after completion of the swallow, but never before 10 sec. If the bolus did not pass, the acquisition was terminated by 60 msec. The lower esophageal sphincter was marked manually on the computer screen. By a dedicated program, the MTT was calculated from the time-activity curves. We used 3 frames/sec during the first 10 sec and 1 frame/sec during the following 50 sec. The time-activity curve was generated from a region of interest (ROI) covering the whole esophagus. The program automatically subtracted an area with an angle of 60° in the lower left corner of the ROI to exclude activity accumulated in the fundus of the stomach. The initial steep rise of the activity curve is followed by a lower plateau as the bolus passes behind the sternum. The initial peak was reduced by a curve fit program after manual indication on the curve to correct for different attenuations above and below the sternum. Background subtraction was not performed. The effective dose equivalent is 0.011 mSv/MBq and the critical organ is the thyroid gland receiving 0.035 Gy/MBq. The MTT is calculated using Zierler's area-over height equation (*23*):

$$\mathrm{MTT} = \frac{\int C(t)dt}{C_{max}},$$

where C is counts per second (cps) and C_{max} is the maximal count rate. Residual activity is calculated after manual indication on the plotted curves as percentage of the maximum activity.

The curves were classified in two different groups: (1) ≤2 spikes, (2) ≥3 spikes. A spike is a secondary steep rise in activity as determined by inspection of the time activity curve.

In 46 of the subjects, the passage of capsules was also examined. Capsugel® No. 1, which has a length of 18 mm and an outer diameter of 7 mm, contained 5 MBq [^{99m}Tc]pertechnetate and five tablets of lactose exactly filling the capsule. The density was >1. The capsules were administered with the patient both in the recumbent and sitting positions. If the activity of the capsule stayed in the esophagus for more than 60 sec, the capsule was considered to be retained, since it is known that only a few capsules will leave the esophagus after 60 sec. Instead of passing through the esophagus they will slowly disintegrate (*24*).

Statistics

Since the MTT and the residual activity did not follow a Gaussian distribution, nonparametric statistics were used to evaluate the variation of the normal range (median, ranges, and 95-percentiles).

TABLE 1
Mean Transit Time (MTT) Values and Residual Activity (RA) from Radionuclide Transit Studies in 49 Healthy Subjects (Supine Position) and 21 Subjects (Sitting Position)

	Supine		Sitting	
	MTT (sec)	RA %	MTT (sec)	RA %
n	49	49	21	21
Median	6.2	10.8	4.5	9.5
95-percentiles	3.7–9.6	2.0–45	3.4–6.1	0–29

The values represent double measurements.

For the evaluation of the interday, intrasubject, intraobserver and interobserver variations of double measurements, the coefficients of variation (CV) were calculated according to the following formula:

$$S^2 = \frac{\Sigma\,(X1-X2)}{2n}$$

$$CV(X) = \frac{S}{\bar{X}} \times 100,$$

where s^2 is the variance. The first and the second measurements were compared by double tailed t-test. One investigator (FJ) evaluated all curves. In the calculation of interobserver variation, two investigators were involved.

RESULTS

The median and 95% percentiles of the single measurements of MTT and residual activity were in the supine position 6.05 (3.2–11.5) sec and 11.5% (3–50) and in the sitting position 4.4 (3.0–6.0) sec and 13.0% (0–30), respectively. The variation of the single measurements for MTT and the residual activity in the sitting and supine positions given as coefficients of variation (cv) were 20%–35% for the MTT and 85%–120% for the residual activity. The intraday variation of double measurements presented as median and 95% percentiles are shown in Table 1. When double measurements were used, the CVs were reduced for MTT to 10% and the residual activity to 40% in the supine position, but the variation of the residual activity was still considerable. The intraday variation is shown in

TABLE 2
Mean Transit Time (MTT) and Residual Activity (RA)

	Intraday variation		Interday variation		Intraobserver variation		Interobserver variation	
	MTT	RA	MTT	RA	MTT	RA	MTT	RA
n	49		49		11		27	
CV%	10	38	12	35	3.4	9	5.7	4.2

Double measurements and double analyses in healthy subjects examined in the supine position. The intraday variation is calculated from single measurements.

Table 2. The intraday variation of the MTT was smaller than the interday variation, but the intraday repeatability of measurements does not differ significantly from day to day measurements (Table 2).

The intraobserver variation of MTT was 3.4% and the variation of the residual activity 9% (Table 2). The interobserver variation of MTT was 5.7% and the residual activity was 9% (Table 2). In Figure 1 the distributions of the double measurements of MTT and residual activity of healthy volunteers are shown. No significant changes in MTT or residual activity in relation to age were found. The first and second swallow in either position have been compared and no significant differences were found ($p = 0.39$).

The influence of age was investigated by comparing three age groups and the result is shown in Figure 2. It is seen that curves with three spikes or more were rare below the age of 40 and quite common above 40 yr, but MTT and residual activity were similar in the three age groups. The influence of age on the passage of capsules is shown in Figure 3. It is shown that capsules lodge more frequently in the supine position. No influence of age was found.

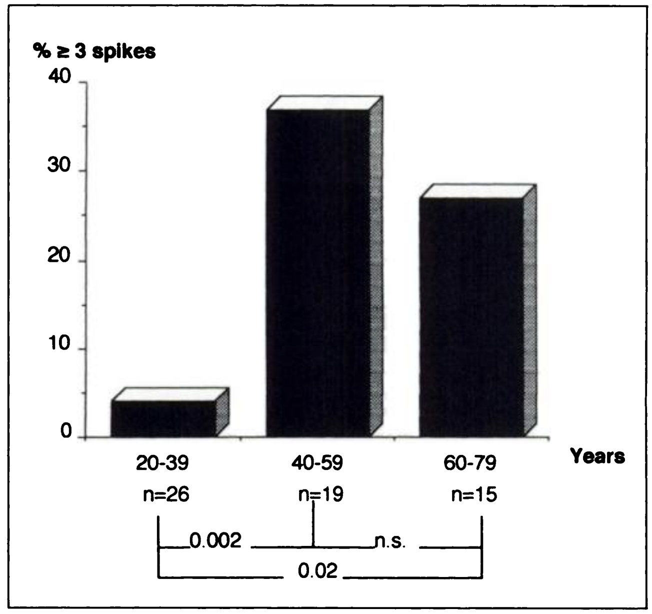

FIGURE 2. Percentage of subjects with more than two spikes per curve in three different age groups. P values are indicated. ns = not significant.

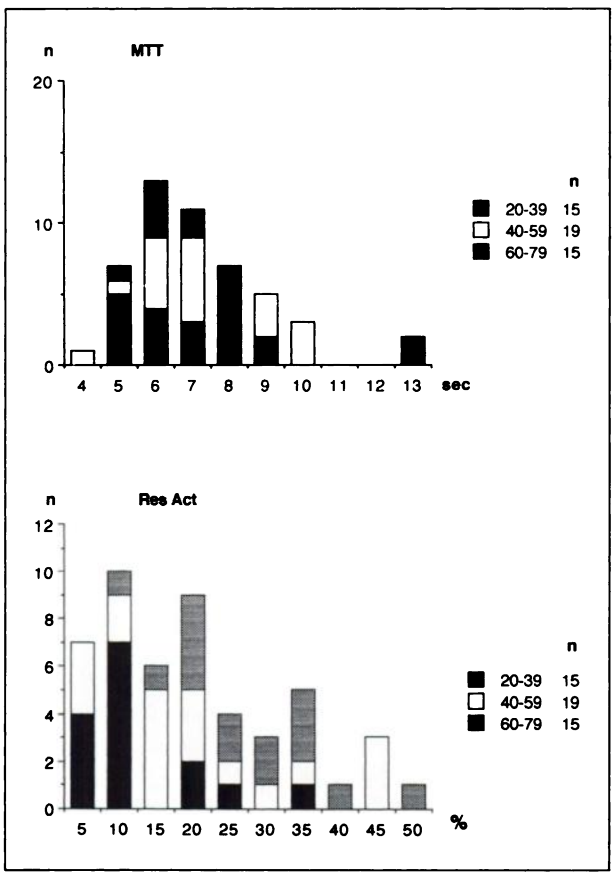

FIGURE 1. The distribution of mean transit time (MTT) and residual activity (res. act.) in the supine position. The mean of the first and the second swallows are presented. The age groups (20–39, 40–59, 60–79 yr) are indicated for each interval. Data from 49 subjects are presented.

DISCUSSION

Esophageal scintigraphy has been performed by several investigators using different techniques and normal ranges have been calculated (*2–10*)). The results of the transit time in the studies of liquid swallowing are similar (from 6 to 10 sec) and the standard deviation is acceptable (1–3 sec). It may be advantageous, but not mandatory, to perform the more cumbersome, repeated swallow technique as double measurements increase the precision to a satisfactory level.

On the other hand, variations of residual activity meas-

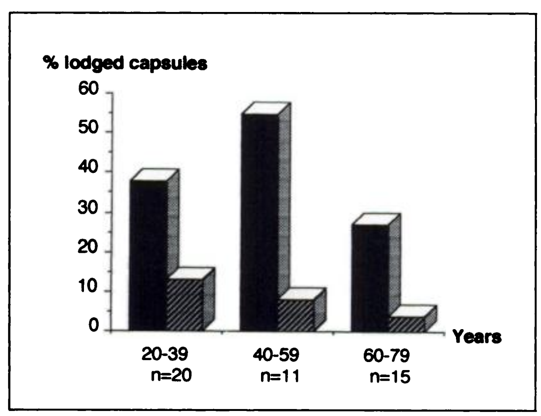

FIGURE 3. Percentage of subjects with lodged capsules in three different age groups. No significant differences were found between age groups. Differences between the supine and sitting positions were significant in all three age groups. Black columns indicate the supine position, hatched columns the sitting position.

urements are quite large in the single swallow method. The normal range is reduced when double measurements are used, but the intrasubject variation is still high in our hands (Table 2). Klein and Wald (*10*) also found a high degree of intrasubject variation with only one swallow, but when a repeated swallow was added after 30 sec the inter- and the intrasubject variation was reduced.

We found no influence of age on MTT or residual activity. The latter has been reported by Klein and Wald (*10*). However, we did find a difference in the frequency of three spikes or more between subjects below and above 40 yr. This is probably related to tertiary contractions, a known age-dependent physiological event and not a marker for esophageal disease. Lodging of capsules has been found to be more frequent in the elderly (*24*), but we did not find any statistical difference.

The importance of the projection has been discussed lately. The posterior projection is preferred by some authors (*25*) due to a more uniform attenuation in the posterior position, although the attenuation is decreased in the anterior position. It is postulated that the measurements are more accurate in the posterior position. With the observed low intra- and interobserver variabilities but high intra- and interday variabilities in mind, this should not be a crucial point in the method.

The use of ^{99m}Tc as pertechnetate or as other labeled compounds is preferred by the majority. The use of ^{81m}Kr has had advocates (*7*) due to the very low radiation dose. In our opinion the radiation dose with ^{99m}Tc is still very low and of no serious concern. Krypton-81m is not available everywhere, and the short half-life is problematic when MTT is prolonged. The same group (*7*) has used the centroid formula to calculate mean transit time. The application of the centroid formula or Zierler's formula has been discussed previously (*22*). Normal values of MTT do not vary much in different studies (*3–8,10,14*). Accordingly, variations in the technique appear less critical. It has been the aim of several investigations to find characteristic patterns in radionuclide transit studies with different esophageal diseases. The efforts have not been fruitful despite many attempts to visualize the swallowing process, most elegantly demonstrated by the application of the method of condensed images (*11*). The reason might be that the method shows little more than the possible delay in esophageal transport whether calculated in one way or another. Therefore the result is probably rather independent of the underlying pathophysiology.

In conclusion, we have shown in 60 healthy subjects that MTT has a rather narrow, age-independent normal range and a good reproducibility, when calculated according to Zierler's formula and corrected for different attenuation above and below the sternum. Our values are similar to those previously reported in small groups of healthy persons. The high intraindividual variation and low reproducibility limit the clinical value of measurement of residual activity.

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