

The diagnostic value of oesophageal transit scintigraphy for evaluating the severity of oesophageal complications in systemic sclerosis

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Background Oesophageal complications are common in systemic sclerosis (SSc). However, the ability to determine the severity of oesophageal complications according to SSc type and skin lesion has not been evaluated.

Methods The study groups consisted of 35 patients with SSc who were classified into diffuse ($n=20$) and limited ($n=15$) cutaneous types, and 16 control subjects. An additional 26 consecutive patients were studied for an analysis of the reproducibility. The severity of a skin lesion was quantified by using a modification of Rodnan's total skin thickness scores. Oesophageal scans were performed after the subjects, in sitting and supine positions, had consumed potage soup. Condensed images of the dynamic study were classified into four patterns: normal, transient retention, slight retention and severe retention, in conjunction with parameters of retention fraction by analysing the time–activity curve.

Results The highest reproducibility was obtained using retention at 90 s (R_{90} , $r=0.93$). Analysis of the condensed images showed that the SSc patients had a higher incidence of severe retention than did the control subjects. Groups with diffuse-type SSc or a high skin thickness score showed a higher incidence of severe retention ($P=0.041$ and 0.0048 , respectively) compared with the

control and less severe groups. The R_{90} in the supine position differed significantly among the controls, the limited-type and diffuse-type SSc groups (mean \pm SEM, $10 \pm 1\%$, $24 \pm 5\%$, $38 \pm 6\%$, respectively; $P=0.0004$). The group with high skin scores (i.e. ≥ 10) showed a higher R_{90} ($41 \pm 6\%$) than did either the group with low skin scores ($R_{90}=23 \pm 5\%$) or the control group ($P=0.0001$).

Conclusion An oesophageal scan can detect both slight and severe types of oesophageal dysfunction, and can be used as a quantitative method that reflects functional abnormality in SSc. *Nucl Med Commun* 25:375–381

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Introduction

Systemic sclerosis (SSc) is a disorder characterized by scleroderma, and involves various organs such as heart, lung, kidney and gastrointestinal tracts [1–5]. Of these generalized disorders, typical oesophageal complications include dysphagia and oesophageal reflux. The symptoms and signs are caused by neuropathy of the gastrointestinal nervous system and collagen deposition or fibrosis in the smooth muscle layer. Although gastrointestinal manifestations are frequent and burdensome to patients with SSc, early subjective gastrointestinal signs such as dysphasia, acid regurgitation or heartburn may be overlooked. Moreover, serial worsening or improvement is difficult to quantify.

Although oesophageal transit scintigraphy has been used as a simple method, in part because it is not uncomfortable for the patients [6–18], the method seems to be

under-utilized in many hospitals. The reasons for this are partly due to poor reproducibility of the scintigraphic results and various kinds of scintigraphic parameters depending on the hospital. Some studies have shown the usefulness of an oesophageal transit study to identify patients with SSc disorders from a normal population [7–13], but no statistical differences have been observed regarding SSc subgroups of different severities. The relationship between oesophageal scintigraphic findings and the severity of the skin lesion has not been defined yet. If some correlation between the disease severity and an oesophageal transit study did exist, scintigraphic parameters could be used for the diagnosis, progression and marker for therapeutic effects.

Thus, the aims of this study were to determine simple and practical transit parameters from time–activity curves and condensed images and to evaluate the relationship

between SSc types and the severity of scleroderma lesions.

Subjects, materials and methods

Patients and controls

Sixty-seven patients were studied by using oesophageal transit. In study I, the group consisted of 35 patients (29 females and six males, average age 53 ± 15 (SD) years) who were diagnosed with systemic sclerosis (SSc) in our department of dermatology based on American Rheumatism Association diagnostic criteria [19], and 16 control subjects. The final diagnosis of SSc was made based on skin lesions and organ involvement including lung, heart, kidney and digestive systems. The classification into diffuse and limited cutaneous SSc types was based on skin lesions, other clinical findings and laboratory data according to LeRoy *et al.* [3]. The severity of scleroderma was scored from 0 (normal) to 3 (severe) in 17 body surface areas using a two-step pinching method. Each skin thickness score was summed and a total skin score was calculated [4,5]. In this study group, the total skin score ranged from 1 to 36 with a mean of 10 ± 10 (SD). Fifteen patients had limited cutaneous type (age 59 ± 9 years) and 20 patients had diffuse cutaneous type (age, 48 ± 17 years). The total skin scores were 4 ± 2 (SD) and 17 ± 9 for limited and diffuse cutaneous types. The skin score of < 10 and ≥ 10 was defined as the low ($n = 17$) and high ($n = 18$) skin score groups, respectively. Antibodies, including anti-topoisomerase I and anti-centromere antibodies, were examined.

The control group consisted of 16 patients (13 females and three males, average age 45 ± 16 years) who were initially suspected of having collagen diseases, but the possibility was discarded after closer examinations. They had no clinical gastrointestinal symptoms and signs. Oesophageal transit scintigraphy was not used for the selection of the control patients.

In study II, the reproducibility of the parameters from time-activity curves was examined in 26 consecutive patients (24 females and two males, average age 51 ± 13 years). The patients were studied twice in the supine position, after consuming soup, as described below. They were diagnosed with SSc ($n = 21$) and mixed connective tissue disease ($n = 5$).

Oesophageal transit study

^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) was mixed with a commercially available powdered potato soup (Ajinomoto Co. Tokyo, Japan) and the concentration was doubled to increase its viscosity. Patients were instructed to retain 7 ml of soup, in which 20–30 MBq of ^{99m}Tc was mixed, and to swallow the soup in one gulp. After 30 s, the patients repeated dry swallows in each 15 s interval (Fig. 1). After practice attempts of several

swallows, the studies were repeated twice with subjects in the sitting and supine positions for consuming the soup. Fragmentation of the bolus in the swallow could be avoided by the practice outlined by Sand *et al.* [16]. The retained activity in the oesophagus, if present, was cleared by drinking water between the studies. Serial anterior images were acquired in 64×64 matrices for 96 s at 0.5 s per frame. A large rectangular field-of-view camera (53×39 cm) equipped with a low energy, high resolution collimator (Toshiba Co., Tokyo, Japan) was used.

Data analysis

After observing tracer transit on a cinematic display, oesophageal transit was analysed by time-activity curves (Fig. 1). Using a temporally summed oesophageal image, a region of interest was set over the whole oesophagus ranging from the upper oesophagus to the gastrooesophageal junction, and a time-activity curve was generated. A parameter of half-time ($T_{50\%}$) was defined as the interval from the peak activity to the emptying of 50% of the maximum count. The $T_{50\%}$ point was determined by linear interpolation of the time-activity points. The retention fraction was defined as the retained activity divided by the maximum activity at 30, 60 and 90 s (R_{30} , R_{60} and R_{90} , respectively).

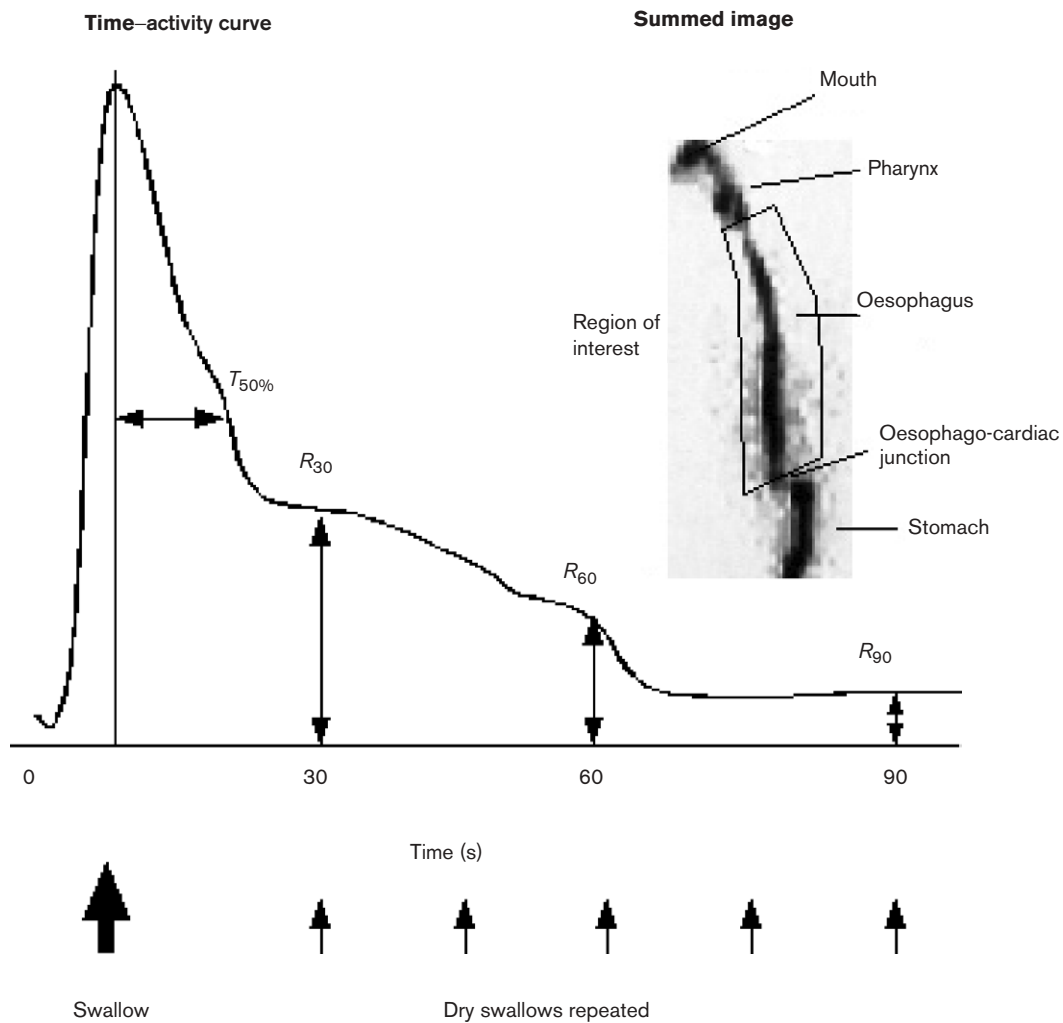
The analysis of condensed images is described elsewhere [6,14,15]. Each frame was compressed to a single column, and the columns were assembled into a condensed image, whose horizontal and vertical directions were temporal and spatial dimensions. Based on the condensed image, we classified the patients into four patterns (Fig. 2), as follows.

- *Normal*: rapid increase and clearance after ingestion, with both R_{30} and $R_{90} \leq 15\%$;
- *transient retention*: transient retention in the oesophagus, with $R_{30} > 15\%$ in the time-activity curve, followed by clearance, with $R_{90} \leq 15\%$ by repeated dry swallows;
- *slight retention*: slight degree of continuous retention with, $R_{90} = 15\text{--}50\%$ in the oesophagus;
- *severe retention*: severe stagnation, with both R_{30} and $R_{90} \geq 50\%$.

Statistics

Values in the results section were expressed as the mean \pm standard error of the mean. The differences of the variance and mean values were examined by a multiple comparison test following a significant finding in the one-way analysis of variance (ANOVA). The differences between the two selected groups were examined by repeated measure models of ANOVA with Fisher's protected least significance difference (PLSD) and Scheffé tests. The difference of the contingency

Fig. 1



An example of the summed image of oesophagus, and a time-activity curve. The value of $T_{50\%}$ and the retention rate at 30, 60 and 90 s (R_{30} , R_{60} and R_{90} , respectively) were calculated.

table was examined by the chi-squared P value. Linear regression analysis was calculated for reproducibility analysis. A P value $< 5\%$ was considered significant.

Results

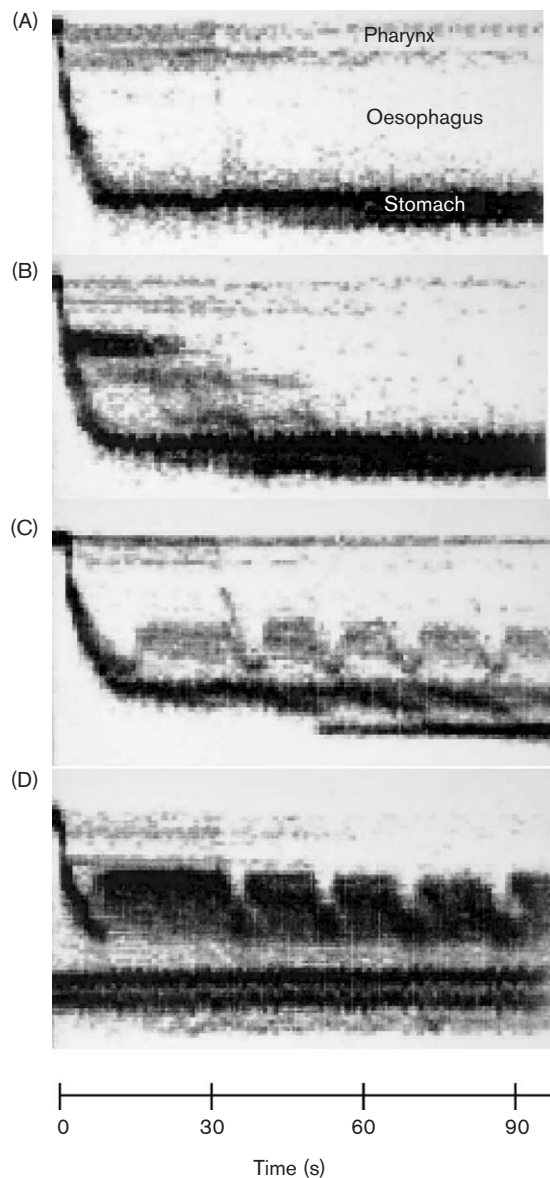
Reproducibility of the parameters

Regarding the reproducibility of the repeated measurements ($n = 26$), the correlation coefficient, R , was 0.59 (regression line $y = 0.67x + 5.2$) for $T_{50\%}$; and 0.68 ($y = 0.64x + 15.0$), 0.69 ($y = 0.73x + 9.9$) and 0.93 ($y = 1.06x + 3.9$) for R_{30} , R_{60} and R_{90} , respectively. The retention fraction ranged from 6% to 91% (average 37%), 5% to 62% (average 30%), and 4% to 74% (average 25%) for R_{30} , R_{60} and R_{90} , respectively. We therefore used R_{90} for the following analysis.

Condensed image patterns

Typical patterns of the condensed images are shown in Fig. 2. Condensed image patterns in the control and SSc groups are compared in Table 1. In the control group, all patients showed either normal or transient retention patterns except for a patient with slight retention in the supine position with soup, while patients with SSc showed a higher incidence of severe retention. Although the study with patients in the sitting position did not reach statistical significance ($P = 0.073$), studies with patients in the supine position revealed significantly higher rates of severe retention when the chi-squared test ($P = 0.01$) was used. Table 2 compares condensed image patterns in the limited and diffuse cutaneous types. Severe retention was observed in zero (0%), four (27%) and nine (45%)

Fig. 2



Typical condensed image patterns. (A) Normal pattern; (B) transient retention pattern; (C) slight retention pattern; and (D) severe retention pattern.

patients in the control, limited and diffuse types, respectively ($P = 0.041$).

Regarding the relationship between the skin score and condensed image patterns, severe retention was observed in zero (0%), three (17%) and ten (77%) patients in the control, low and high skin score groups, respectively ($P = 0.0048$). When the sitting and supine positions were compared in the total 51 patients, the patterns of normal, transient retention, slight retention and severe retention were seen in 20, 14, 4 and 13 patients in the supine

Table 1 Condensed image patterns in the control and systemic sclerosis (SSc) groups

Group and pattern	Sitting	Supine
Control		
Normal	15	11
Transient retention	1	4
Slight retention	0	1
Severe retention	0	0
Systemic sclerosis		
Normal	20	9
Transient retention	10	10
Slight retention	3	3
Severe retention	2	13
Chi-squared P value between controls and SSc	NS	0.010

Table 2 Relationship between systemic sclerosis (SSc) types and condensed image pattern with patients in the supine position

	Normal	Transient retention	Slight retention	Severe retention	Total
Control	11	4	1	0	16
SSc type*					
Limited	5	5	1	4	15
Diffuse	4	5	2	9	20
Skin thickness score**					
Low	7	5	2	3	17
High	2	5	1	10	18
Total	20	14	4	13	51

Chi-squared * $P = 0.041$; ** $P = 0.0048$.

position, and the patterns were seen in 35, 11, 3 and 2 patients in the sitting position, respectively. Patients in the supine position showed a higher incidence of severe retention than did those in the sitting position ($P = 0.0025$).

Retention fraction

The parameter of R_{90} is shown in the control, in each SSc type and low and high skin score groups (Table 3). A significant difference was observed among control and SSc types ($P = 0.016$ and 0.0004 for the sitting and supine positions, respectively) and also among control and low and high skin scores ($P = 0.046$ and < 0.0001 for the sitting and supine positions, respectively). When a mean greater than +2 standard deviations was considered abnormal, the upper limits of R_{90} were 11% and 22% for the sitting and supine conditions, respectively. Using these criteria in the sitting position, one of 16 (6%), two of 15 (13%) and 10 of 20 (50%) patients were judged as abnormal ($P = 0.005$) in the control, limited and diffuse types, respectively.

Regarding skin thickness scores, four of 17 (24%) and eight of 18 (44%) patients were abnormal in the low and high skin score groups ($P = 0.038$), respectively. In the

Table 3 Retention at 90 s (R_{90} values) in the control and systemic sclerosis groups, and the statistical significance

Group	<i>n</i>	Sitting	Supine
Retention at 90 s*			
Control	16	5.6 ± 0.6	10.1 ± 1.4
SSc type			
Limited	15	7.8 ± 1.6	23.7 ± 4.9
Diffuse	20	13.7 ± 2.7	37.8 ± 5.6
Skin thickness score			
Low	17	9.1 ± 1.9	22.5 ± 4.8
High	18	13.1 ± 12.0	40.6 ± 5.6
Statistical significance (<i>P</i> values)			
SSc type			
ANOVA		0.016	0.0004
Fisher PLSD		C, dSSc (0.006); dSSc, ISSc (0.047) C, dSSc (0.022)	C, dSSc (<0.0001); dSSc, ISSc (0.036) C, dSSc (0.0004)
Scheffé			
Skin thickness score			
ANOVA		0.046	<0.0001
Fisher PLSD		C, H (0.014)	C, H (<0.0001); L, H (0.0056)
Scheffé		C, H (0.047)	C, H (<0.0001); L, H (0.021)

*Values are given as the mean ± SEM. SSc, systemic sclerosis; PLSD, protected least significance difference; C, control; ISSc, limited-type SSc; dSSc, diffuse-type SSc; L, low skin score; H, high skin score.

supine position, one of 16 (6%), five of 15 (33%) and 14 of 20 (70%) patients were judged as abnormal ($P = 0.0004$) in the control, limited and diffuse types, respectively. Similarly, regarding skin scores, five of 17 (29%) and 14 of 18 (78%) patients were abnormal in the low and high skin score groups ($P < 0.0001$), respectively.

Serum autoantibodies

When patients were classified into anti-topoisomerase I antibody positive ($n = 12$) and negative ($n = 23$) groups, the former showed slightly higher R_{90} ($42.1 \pm 7.3\%$ vs $26.3 \pm 4.4\%$, $P = 0.057$). Regarding anti-centromere antibody positive ($n = 11$) and negative ($n = 24$) groups, no statistically significant difference was observed between the groups.

Discussion

Although several parameters have been used for quantifying oesophageal transit, the reproducibility of parameters has been considered critical in oesophageal scintigraphy. Fundamental data analysis of oesophageal transit is based on either a global oesophageal region and/or separate regions outlined around the hypopharynx and proximal, middle and distal regions [20,21]. The parameters of the oesophageal transit study included intervals between the peaks of each region, residual oesophageal activity and emptying time, such as half-time and the time to reach 1/10 of the peak activity. Intra-subject variation between repeat swallows, however, showed significant differences in studies using both liquids and solids. Tatsch *et al.* [8] found a remarkable variation in normal subjects and an even higher variation in patients with disorders based on a single-swallow test, and recommended a sum image with multiple swallows. Edenbrandt *et al.* [9] used residual activity at 12 or 25 s after the beginning of the swallow,

and the time from the onset to 50% emptying. They found that visual analysis was best reflected by the residual activity 25 s after the beginning of the swallow without background correction, but high variability in oesophageal motility was still observed. To overcome intra-subject variation, we tried to determine simple but reproducible parameters in this study. Our protocol used only one swallow but was followed by repetitive dry swallows in each 15 s interval as Klein [13] and Klein *et al.* used [20]. When residual activities at 30 s, 60 s and 90 s were compared, the reproducibility increased with time after ingestion. The R_{90} revealed a sufficiently high correlation coefficient ($r = 0.93$). Although use of R_{90} may have decreased a true-positive rate compared with R_{30} , we decided to use R_{90} to obtain steady results.

Condensed image analysis was also an effective way to view transit patterns and showed good correlation to the severity of the scleroderma. In the control subjects, 11 of 16 (69%) patients showed a normal pattern, and the remaining five patients (31%) showed transient or slight retention patterns. No control subject showed more than 50% retention throughout the 30 to 90 s time period, although some overlap may exist in patients with the transient retention.

The position of the patients and types of ingested material may have influenced the results. Although the erect or sitting position was considered to be more physiological, the supine position was preferred in order to detect early oesophageal motility disorders. Because severe retention was rare in the sitting position, the patterns did not differ significantly between the control and SSc patients. Significant stagnation, however, was seen when patients with SSc were in the supine position.

The supine position is almost totally dependent on oesophageal motility rather than gravity, and may unmask earlier oesophageal dysmotility.

The originality of this study was that we were able to discriminate the severity of the SSc complication. The severity of the SSc, however, could not be differentiated well in the previous oesophageal transit studies. Bestetti *et al.* studied 18 patients with SSc and demonstrated no significant difference between limited and diffuse cutaneous types [7]. Klein *et al.* studied 17 patients with SSc, including nine limited and eight diffuse cutaneous types [13]. However, they also found no significant difference between the types. In contrast, the present study indicated a significantly high retention fraction in the diffuse cutaneous type SSc. The difference in the high and low skin score groups also supported the adequacy of R_{90} for discriminating disease severity. Another reason for the statistical significance may be that we examined a larger number of SSc patients than in the previous studies. Positive anti-topoisomerase I antibody, which has been known to indicate the severity of SSc lesions, showed a slightly higher R_{90} , although the P value was borderline (0.057).

The incidence of abnormal R_{90} was 54% (19 of 35) in the supine position. Slight or severe retention patterns were seen in about 46% (16 of 35) of patients with SSc. Medsger *et al.* described the incidence of gastrointestinal involvement in approximately 70% of the subjects he examined [2]. D'Angelo *et al.* investigated 48 autopsy cases and found that 74% showed muscle atrophy and/or fibrosis in the oesophagus [1]. Our results showed a lower incidence of abnormality. This is partly because the population of the present study included a less severe form of SSc than was found in the autopsy patients, and involvement of the other parts of intestinal tracts was not evaluated in this study. In addition, the total skin score of ≤ 36 in this study has been generally considered to be of slight-to-moderate degree and no patient with severest form was included. The racial differences in the incidence of complication can be another factor of variability [22].

In terms of the survival of the patients with SSc, pulmonary, cardiac and renal involvements have been considered important. Although gastrointestinal involvement may not be a direct cause of death, association of oesophageal hypomotility and pulmonary function impairment has been noted [18,23]. Cardiac involvement is also common in SSc patients, and cardiovascular autonomic dysfunction may be associated with motor dysfunction [24,25]. Therefore, multiple-organ involvement should be carefully assessed, and quantitative methods are important for the determination of risk stratification.

We could not evaluate the true-positive rate, because no definitive diagnosis was given regarding oesophageal dysfunction and subjective complaints were diverse. Oesophageal manometry could not be performed in this population. Roland *et al.* showed that the radionuclide swallow test was as good as manometry in patients with slight or moderate oesophagitis [17]. Moreover, the good correlation with the severity of the skin lesion and SSc types in the present study supports the validity of this approach. Further studies in the follow-up of patients and prognostic value should be investigated, since our study showed a high reproducibility with a simple methodology that can be utilized in any hospital.

Conclusion

Oesophageal scintigraphy was performed in control and SSc patients. The retention rate at 90s assessed in the supine position revealed a high reproducibility and diagnostic usefulness for discriminating normal and disease conditions as well as the severity of oesophageal complications.

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