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Esophageal hypomotility in systemic sclerosis: Close relationship with pulmonary involvement

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Purpose: Esophageal motility was assessed in patients with systemic sclerosis (SSc) by scintigraphy and compared with (i) extent of scleroderma, (ii) duration of disease, (iii) index of anti-topoisomerase I antibody (topo I), and (iv) pulmonary involvement. ***Methods:*** A multiple-swallow test was performed in 47 patients with SSc in the supine position with ^{99m}Tc-DTPA. A region of interest on the entire esophagus was defined and the retention ratio (RR) was calculated from a time-activity curve. ***Results:*** Patients with diffuse scleroderma had higher RRs than those with limited scleroderma (48.8% vs. 30.0%; $p < 0.05$). There was no correlation between the RRs and the duration of disease. Patients with positive topo I had higher RRs than those who were negative (53.8% vs. 29.7%; $p < 0.05$). Patients with reduced % diffusion capacity for carbon monoxide (%DL_{CO}) had higher RRs than those with normal %DL_{CO} (40.5% vs. 19.6%; $p = 0.03$). Patients with reduced % vital capacity (%VC) had higher RRs than those with normal %VC (54.6% vs. 25.0%; $p < 0.005$). Patients with pulmonary fibrosis had higher RRs than those who were negative (58.5% vs. 20.3%; $p < 0.00005$). ***Conclusion:*** Esophageal dysfunction in patients with SSc showed a correlation with the extent of scleroderma, positive topo I, and pulmonary involvement. The RR can be an objective clinical marker for the severity of organ fibrosis.

Key words: esophageal scintigraphy, systemic sclerosis, esophageal hypomotility, anti-topoisomerase I antibody, pulmonary involvement

INTRODUCTION

SYSTEMIC SCLEROSIS (SSc) is characterized by fibrosis and vascular obliteration in the skin, gastrointestinal tract, lungs, heart and kidneys.[1] Esophageal involvement is common and found in 75% of patients.[2] The characteristics of esophageal lesion in SSc are smooth muscle atrophy and fibrosis of the lower two-thirds of the esophagus.[3] It is important to assess esophageal motility because esophageal dysfunction is one of the most serious conditions adversely affecting the quality of life of patients with SSc.

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For the detection of impaired esophageal motility, esophageal manometry has been recognized as a gold standard, but it is troublesome because of the catheter procedure. Scintigraphy has been reported to be useful and as sensitive as manometry,[4–10] and it is more easily performed and less invasive. Furthermore, it is possible to examine esophageal hypomotility by quantitative assessment.

It is generally accepted that there are a number of clinical subsets in SSc. Barnett suggested 3 types of classification according to the extent of sclerosis,[11] and LeRoy and Medsger proposed 2 types: a stable, limited cutaneous group representing the majority of patients and a more rapidly advancing smaller group with diffuse cutaneous involvement.[1] There are several kinds of autoantibody specific to SSc and they provide information about the clinical course of each patient.[12–15] Anti-topoisomerase I antibody (topo I) is present in 21–26% of

patients with SSc,[12,13] and associated with severe peripheral vascular disease, a high incidence of pulmonary fibrosis and poor prognosis.[12,16,17]

One of the major causes of death in SSc is pulmonary involvement.[1,3,11,18] At autopsy, interstitial fibrosis is commonly found,[4] but its natural history has not been fully understood and it is difficult to give patients accurate information on pulmonary involvement.[18–23]

In this study we performed esophageal scintigraphy to obtain an objective index of esophageal motility and compared it with the extent of skin sclerosis, the duration of the disease, topo I index and pulmonary involvement to better understand the clinical course of patients with SSc.

SUBJECTS AND METHODS

Subjects

Ten normal volunteers (2 women, 8 men; mean age 36 years; range 27–48) and 47 patients (42 women, 5 men; mean age 51 years; range 10–68) with SSc were enrolled in the study. The diagnosis of SSc was based on the criteria of the American Rheumatism Association. According to the classification by LeRoy and Medsger,[1] 26 patients were classified as the limited cutaneous type and 21 as the diffuse cutaneous type. According to the classification by Barnett,[11] 11 patients were classified as type I (skin changes in fingers only), 20 as type II (skin changes beyond the fingers but mainly in the extremities) and 16 as type III (diffuse). Disease duration after the initial diagnosis ranged from 3 months to 30 years (mean 7.5 years). One patient was diagnosed with CREST syndrome.

Protocol

Esophageal scintigraphy was performed in the supine position after a 5-hour fast. The examinee swallowed 10 MBq of Technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) in 5 m*l* of saline once on command. 30 sec after swallowing, they were instructed to do 5 dry swallows every 15 sec. 0.5 sec/frame scintigraphic data of were obtained in a 64 × 64 matrix for 96 sec with a rectangular large-field of view camera (GCA-90B, Toshiba, Tokyo, Japan). To assess the reproducibility of the procedure, 11 patients underwent a repeat examination a few days later.

Data analysis

A region of interest over the whole esophagus was defined and a time-activity curve was generated. The retention ratio (RR) was the percentage of the count at 95.5–96.0 sec to the maximum count after background correction. The count over the entire esophagus before the initial swallow was used as the background activity.

Comparison of normal volunteers and patients

The RRs of normal volunteers and patients were compared to determine if RRs reflect esophageal motility.

Correlation between extent of skin sclerosis, disease duration, index of topo I and RR

To see if any correlation between the extent of scleroderma and esophageal dysfunction would be found, RRs were compared according to the classification either by LeRoy and Medsger or Barnett. Disease duration after the initial diagnosis and index of topo I were also compared with the RR. Determinations of the topo I index was done by the enzyme-linked immunosorbent assay method (MESACUP Scl-70 test, MBL, Nagoya, Japan) and an index of topo I over 10 was regarded as positive.[15]

Correlation between pulmonary involvement and RR

Information on the % diffusion capacity for carbon monoxide (%DL_{CO}) and the % vital capacity (%VC) were obtained and compared with RRs. A %DL_{CO} under 80% and a %VC under 80% were regarded as abnormal.[24] Pulmonary fibrosis was determined as the increase in interstitial shadows on X-ray computerized tomograms (X-CT) 10 mm thick (GE 9800CT, General Electric Co., Milwaukee, WI), which were assessed by radiologists who were unaware of the results of the scintigraphic study.

Statistical analysis

Data are expressed as the mean ± standard deviation (s.d.). The results were compared by unpaired Student's t-test, Welch's t-test and analysis of variance (ANOVA). In the analyses, the level of significance was set at 5%.

Table 1 Relationship between the extent of scleroderma and the retention ratio (RR)

	n	RR (%)
LeRoy & Medsger		
limited cutaneous type	26	30.0 ± 29.6
diffuse cutaneous type	16	48.8 ± 33.1*
Barnett		
type I	11	22.0 ± 26.8
type II	20	30.4 ± 31.0
type III	16	56.3 ± 30.7**

mean ± s.d.

* Significant vs. RR of limited cutaneous type ($p < 0.05$)

** Significant vs. RR of type I patients ($p < 0.05$) and RR of type II patients ($p < 0.05$)

Table 2 Relationship between the duration of the disease and the retention ratio (RR)

duration (year)	n	RR (%)
Under 5	25	42.8 ± 30.8
5–10	7	20.4 ± 29.7
Over 10	15	40.1 ± 34.9

mean ± s.d.

No significant difference is observed.

Table 3 Relationship between pulmonary involvement and the retention ratio (RR)

	n	RR (%)
$\%DL_{CO}$		
normal	14	19.6 ± 25.6
reduced	30	40.5 ± 29.2*
%VC		
normal	31	25.0 ± 24.1
reduced	15	54.6 ± 33.6**
pulmonary fibrosis		
negative	22	20.3 ± 21.0
positive	23	58.5 ± 30.1***

mean ± s.d.

* Significant vs. RR of normal $\%DL_{CO}$ ($p < 0.05$)

** Significant vs. RR of normal %VC ($p < 0.005$)

*** Significant vs. RR of negative pulmonary fibrosis ($p < 0.00005$)

RESULTS

Comparison of normal volunteers and patients

The maximum counts in the entire esophagus were 400–600 counts/0.5 sec after background correction in both patients and normal volunteers. Patients had higher RRs than normal volunteers (38.4% ± 32.2% vs. 10.4% ± 10.0%; $p < 0.0001$). The results of the repeat examination did not statistically vary from those of the first examination, indicating the reproducibility of this procedure.

Correlation between extent of skin sclerosis, disease duration, titer of topo I and RR

According to the LeRoy & Medsger classification of the extent of scleroderma, patients with diffuse cutaneous sclerosis had significantly higher RRs than patients with limited cutaneous sclerosis (Table 1). As to the Barnett classification, patients with type III showed statistically higher RRs than those with type I or type II (Table 1). There was no correlation between the RRs of patients and the duration of the disease (Table 2). Patients with positive topo I had higher RRs than patients who were negative (53.8% ± 30.7% vs. 29.7% ± 30.8%; $p < 0.05$).

Correlation between pulmonary involvement and RR

Patients with reduced $\%DL_{CO}$, reduced %VC, and pulmonary fibrosis on X-ray CT had higher RRs than those with normal $\%DL_{CO}$, normal %VC, and normal findings on X-ray CT, respectively (Table 3). There was a negative correlation between $\%DL_{CO}$ and RRs (Fig. 1). There was also a weak negative correlation between %VC and RRs (Fig. 2).

DISCUSSION

Scintigraphy with a single swallow has been widely used to assess esophageal motility, but this method showed remarkable intra-individual variations both for patients and normal subjects.[25–27] Klein reported a good correlation between the residual fraction on scintigraphy after four swallows in the supine position and the functional parameters obtained by cine-esophagography and manometry.[28] The patient position is also one of the factors that influence the accuracy of the examinations. Davidson et al. noted that esophageal transit became normal in the majority of patients in the upright position because of gravity.[29] Based on these reports, we assessed patients with a multiple swallow test in the supine position in this study.

Correlation with the extent of skin sclerosis and esophageal hypomotility according to the two different classifications indicated that the incidence of esophageal involvement would be greater in patients with extended skin sclerosis than in those with a limited form.

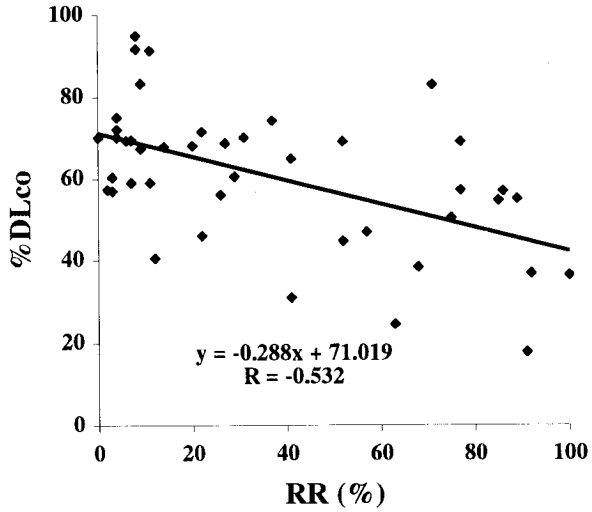

Fig. 1 Relationship between % diffusion capacity of carbon monoxide ($\%DL_{CO}$) and the retention rate (RR) (n = 43).

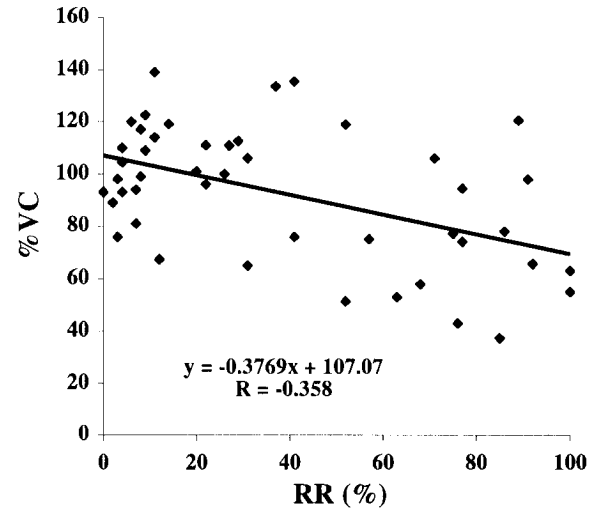

Fig. 2 Relationship between % vital capacity (%VC) and the retention rate (RR) (n = 46).

It has been reported that esophageal abnormalities assessed by scintigraphy would be correlated with disease duration in SSc.[30,31] In our study, however, there was no correlation between esophageal hypomotility and disease duration. It is possible that the severity of esophageal dysfunction would vary among different clinical subsets. Since we did not have enough patients to assess the relationship between disease duration and esophageal function according to each clinical subset, this problem remains to be solved.

Catoggio et al. reported that topo I was not associated with esophageal abnormality when examined radiologically,[13] but we found that the close relationship between esophageal hypomotility and the presence of topo I, indicating that the quantitative analysis by means of the scintigraphic study would be superior to radiographic examination in detecting esophageal dysfunction.

Pulmonary involvement, as well as renal and cardiac involvement, is one of major factors determining the mortality of SSc patients. The presence of topo I means high probability of predicting pulmonary fibrosis,[17] but its natural history has been controversial. Greenwald reported over indolent progression of SSc-related lung disease with substantial individual variation.[18] Colp et al. suggested that it occurs once only and then remains relatively static.[20] Bagg et al. believed that its process is progressive, although usually slow.[21]

We found that pulmonary involvement such as decreased %VC, decreased %DL_{CO} and pulmonary fibrosis are closely related to esophageal hypomotility. Denis et al.[32] and Johnsons et al.[33] attributed the cause of pulmonary fibrosis to proximal gastroesophageal reflux and aspiration.[32,33] This could be one of the causes, but the relationship between the extent of skin sclerosis, topo I and esophageal hypomotility rather indicated that a systemic fibrotic process might occur simultaneously in all these organs in each patient.

It is important to predict the clinical course and prognosis of the individual patient. Barnett reported that the expected survival rate was much higher for types I and II than type III.[11] LeRoy and Medsger also revealed that prognosis for survival from onset of the disease is significantly reduced in diffuse cutaneous type SSc.[1] Pulmonary involvement and positive topo I also provide useful information to predict a severe natural course of the disease. The fact that esophageal hypomotility is frequently accompanied by skin and pulmonary abnormalities suggests that the risk of poor prognosis would be greater in patients with esophageal hypomotility than in those without hypomotility. The close relationship between these factors and esophageal hypomotility shown in the present study would support this hypothesis. The index obtained by esophageal scintigraphy would be a practical and objective clinical marker for the severity of multiple organ fibrosis and may have a prognostic value in patients with SSc.

CONCLUSION

Esophageal scintigraphy with a multiple-swallow test in the supine position is easy to perform, non-invasive and able to provide objective parameters. This study revealed that esophageal dysfunction had a close relationship to the extent of skin sclerosis, positive topo I and pulmonary involvement, suggesting that the involvement of these organs would simultaneously occur. The RR might be an important clinical marker for the severity of organ fibrosis, and may have a prognostic value in patients with SSc.

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