Original Article

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Finger sweating levels evaluated by video capillaroscopy system are increased in patients with systemic sclerosis compared to pre-clinical stage patients

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SUMMARY New strategies for early diagnosis and careful follow-up of systemic sclerosis are urgently needed. We unconventionally used a video capillaroscopy system to measure the amount of sweating on finger pads, and investigated its clinical significance. Thirty-three Japanese patients who were diagnosed with typical or pre-clinical stage patients of systemic sclerosis were included in this study. Five healthy subjects were also included. Among twenty-one patients with typical systemic sclerosis that fulfilled ACR/EULAR 2013 classification criteria, seven had increased sweating levels. On the other hand, among twelve pre-clinical stage patients that did not fulfill the classification criteria, no patient showed increase in finger sweating. We found that there was statistically significant difference. The ratio of diffuse cutaneous systemic sclerosis was also found to be significantly higher in subjects with increased amounts of sweating than in subjects with normal levels. Furthermore, the positivity of topoisomerase I antibody was statistically higher in patients with increased sweating levels than in those without. These results indicated that measurement of finger sweating levels may be a useful tool for early diagnosis and clarification of pathogenesis in this disease.

Keywords capillaroscopy, sweat, systemic sclerosis, skin, collagen, topoisomerase I antibody

1. Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by vasculopathy and excess collagen accumulation in the skin or various internal organs including the lungs and esophagus. Because pathogenesis of SSc remains unknown, diagnosis and treatment is sometimes difficult. However, progressive collagen deposition seen in SSc is often irreversible, at least clinically, and there is an urgent need to develop new strategies of early diagnosis and careful follow-up.

For that purpose, we previously reported that low serum CA9 concentration and microRNA-29 in pre-clinical stage SSc may be utilized as early diagnostic markers (*1,2*). On the other hand, accumulation of thickened collagen in SSc dermis is known to cause atrophy of the sweat glands. In the current study, we focus on the possibility that sweat volume may also be useful for early diagnosis, which has never been investigated before. We unconventionally used a video capillaroscopy system as a novel mean of evaluating sweating levels. Generally, this system is used to detect red blood cell flow by a hand-held microvideoscope. It can also be used to observe the surface of the skin to a depth of up to 2 mm (*3*). We measured the sweating levels on finger pads by this system, and investigated its clinical significance in SSc patients with the idea of possible future application for making early diagnosis and for clarification of pathogenesis of systemic sclerosis.

2. Materials and Methods

2.1. Clinical assessment and patients' material

Thirty-three Japanese patients who were suspected as having SSc were included in this study. Among them, twenty-one patients (nineteen females and two males) fulfilled ACR/EULAR 2013 classification criteria (*4*). These patients with typical SSc were grouped according to the classification system proposed by LeRoy, *et al.* (*5*). Fifteen patients were limited cutaneous systemic sclerosis (lcSSc), while six patients had diffuse cutaneous systemic sclerosis (dcSSc). Clinical and laboratory data

Table 1. Summary of clinical/serological features in patients with typical systemic sclerosis (n = 21)

Males : Females	2:19
Age at the time of capillaroscopy (mean years)	67.5
Duration of disease (mean months)	113.7
Type (diffuse:limited)	6:15
Clinical features	
Pitting scars	28.6
Ulcers	14.3
Nailfold bleeding	61.9
Telangiectasia	38.1
Contracture of phalanges	42.9
Diffuse pigmentation	14.3
Short SF	42.9
Sicca symptoms	52.4
Organ involvment	
Pulmonary fibrosis	28.6
Mean %VC	87.2
Mean %DLco	78.1
Pulmonary hypertension	14.3
Esophagus	38.1
Heart	14.3
Kidney	0.05
Joint	38.1
ANA Specificity	
Anti-topoisomerase I	23.8
Anti-centromere	76.2

Unless indicated, values are percentages. SF: sublingual frenulum, VC: vital capacity, DLco: diffusion capacity for carbon monooxidase, ANA: antinuclear antibodies, Anti-topoisomerase I: anti-topoisomerase I antibody, Anti-centromere: anti-centromere antibody.

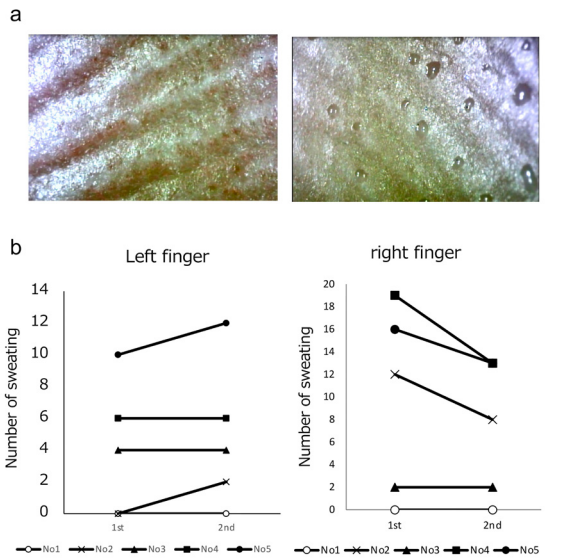

Figure 1. Reproductivity of sweating levels on the finger pads of five healthy subjects. (a) Representative capillaroscopic images of the fourth finger in healthy subjects. Left: image of poor sweating (subject no. 3), right: image of abundant sweating (no. 4). **(b)** Total number of secreting sweat gland on left and right fourth fingers of five healthy subjects (no. 1-5) are shown on the ordinate. The sweating levels were evaluated by capillaroscopy twice (first and second).

were obtained at the time of the evaluation of sweating levels (Table 1). Five healthy subjects (three females and two males) were also included in this study.

This study was approved by the Wakayama Medical University Institutional Review Board (No.2542), and written informed consent were obtained before patients and healthy volunteers were entered into this study, in accordance with the Declaration of Helsinki.

2.2. Measurement of sweating levels

Sweating was evaluated using capillaroscopy (BSCAN-Pro, Toku Corporation, Tokyo, Japan) at 25°C in all patients and healthy subjects (*5*). Number of secreting sweat glands was counted on the three sides (front, left and right sides) of the fourth finger pads for five seconds each, and the total number of sweating was recorded.

2.3. Statistical analysis

Statistical analysis was carried out with Fisher's exact probability test to compare percentages by using Excel 2011 spreadsheet (Microsoft Corp., Redmond, WA) and Statcel4 (OMS, Tokorozawa, Japan). $P < 0.05$ was considered significant.

3. Results

3.1. Reproducibility of sweating levels on finger pads

In this study, capillaroscopy was used according to the protocol of nailfold observation (*6*), and sweating ability was evaluated at 25°C.

The fourth finger was chosen as the site of examination, because many changes characteristic to SSc (*e.g.* round finger pad sign and nailfold capillaroscopic abnormalities) are known to predominantly appear on fourth finger (*7,8*). Representative capillaroscopic video images of fourth fingertip in healthy subjects showed both little (Figure 1a, left) and abundant (Figure 1a, right) sweating levels in each healthy subject, indicating individual differences.

Because this is the first report to evaluate sweating using capillaroscopy, we attempted to prove its reproducibility. Number of secreting sweat glands within a fixed area (width = 1 mm) for total fifteen seconds was counted on the three sides (front, left and right sides) of the fourth finger pads, and the total number of sweating was compared between first evaluation and second evaluation (duration: 1-15 days) in five healthy subjects (No. 1-5, two males and three females with the ages ranging between 34 and 40 years) (Figure 1b).

The difference of finger sweating levels between the two evaluations were < 5 in both the left and right fingers of each individual, indicating the reproducibility of finger sweating levels by our method.

3.2. Comparison of finger sweating levels in patients with typical and pre-clinical stage of SSc

Based on the above results, we measured the finger sweating levels in patients with typical and pre-clinical

stage of SSc (n = 33). Total number of secreting glands of left and right finger sweating levels were recorded.

When the cut-off value was set at 10 secreting glands, in twenty-one patients with typical SSc (male:female = 2:19) who fulfilled ACR/EULAR 2013 classification criteria (criteria score ≥ 9 points), seven had increased amount of sweating (Table 2). On the other hand, among twelve pre-clinical stage patients (all female) that did not fulfil ACR/EULAR 2013 classification criteria (criteria score ≤ 8 points), no patient had increased finger sweating levels. There was statistically significant difference (p = 0.029 by Fisher's exact probability test). Only one typical SSc fulfilled 2016 ACR/EULAR classification criteria for primary Sjögren's syndrome (*9*), but the finger sweating levels of the patient was 20 and not reduced. Our results suggest that finger sweating levels were increased in typical SSc that fulfilled the criteria compared with those in the pre-clinical stage of SSc.

Table 2. Comparison of finger sweating levels between typical and preclinical early stage of systemic sclerosis

	Preclinical stage Criteria score ≤ 8	Typical systemic sclerosis Criteria score ≥ 9
Sweating levels ≤ 9	12	14
Sweating levels ≥10	0	7

Criteria score was calculated based on American College of Rheumatology (ACR)/ European League against Rheumatism (EULAR) 2013 classification criteria. Sweating levels was sum of total number of finger sweating levels.

3.3. Correlation between sweating levels and clinical features in SSc

Lastly, we examined the correlation of finger sweating levels with clinical and serological features in patients with typical SSc who fulfilled ACR/EULAR 2013 criteria (n = 21). Summary of clinical/laboratory features of patients enrolled in this study are shown in Table 1. Mean age was 67.5 years, and patients comprised six dcSSc and 15 lcSSc.

In seven patients with increased sum finger sweating levels, the mean disease duration (between symptom onset and first visit to the hospital) was 72.0 months (Table 3). Meanwhile, in subjects with normal sweating, mean disease duration was 134.6 months. Thus, patients with increased sweating tended to have a shorter disease duration, albeit insignificant. In addition, the ratio of dcSSc was significantly higher in patients with increased sweating levels than in those with the normal sweating levels (dcSSc: lcSSc = 6:1 *vs.* 0:14, p = 0.00013 by Fisher's exact probability test). Furthermore, the positivity of topoisomerase I antibody was statistically higher in patients with increased sweating levels than those without (57.1 *vs.* 7.1%, p = 0.025).

Accordingly, among patients with typical SSc, those with dcSSc and positive for anti-topoisomeraseIantibody

Table 3. Correlation of clinical/serological features and finger sweating levels in typical systemic sclerosis

	Increased sweating (n = 7)	Normal sweating (n = 14)	p value
Males : Females	1:6	1:13	N.S.
Age at the time of capillaroscopy (mean years)	61.1	70.7	N.S.
Duration of disease (mean months)	72.0	134.6	N.S.
Type (diffuse:limited)	6:1	0:14*	p = 0.00013
Clinical features			
Pitting scars	28.6	28.6	N.S.
Ulcers	14.3	14.3	N.S.
Nailfold bleeding	71.4	57.1	N.S.
Telangiectasia	28.6	42.9	N.S.
Contracture of phalanges	57.1	35.7	N.S.
Diffuse pigmentation	14.3	14.3	N.S.
Short SF	57.1	35.7	N.S.
Sicca symptoms	28.6	64.3	N.S.
Organ involvement			
Pulmonary fibrosis	57.1	14.3	N.S.
Mean %VC	76.8	92.5	N.S.
Mean % DLco	64.3	85.0	N.S.
Pulmonary hypertension	0	21.4	N.S.
Esophagus	28.6	42.9	N.S.
Heart	0	21.4	N.S.
Kidney	0	7.1	N.S.
Joint	14.3	50.0	N.S.
ANA Specificity			
Anti-topoisomerase I	57.1	7.1	p = 0.025
Anti-centromere	42.9	92.9	N.S.

Unless indicated, values are percentages. SF: sublingual frenulum, VC: vital capacity, DLco: diffusion capacity for carbon monooxidase, Anti-topoisomerase I: anti-topoisomerase I antibody, Anti-centromere: anti-centromere antibody. *p < 0.05 by Fisher's exact probability test. N.S. : not significant.

tended to have increased finger sweating. Thirteen out of 21 patients with typical SSc were administrated with vasodilators. However, there were no significant association between sweating levels and the use of vasodilators.

4. Discussion

Sclerotic skin lesions of patients with SSc are known to be characterized by histopathologically thickened and increased collagen bundles, which makes sweat glands atrophic or absent (*10*). Sweating of SSc patients is therefore believed to be decreased, and no reports have yet proven abnormal sweating levels in SSc patients.

In this study, we directly measured sweat secretion of SSc fingers using capillaroscopy and present three major findings. Firstly, we proposed a novel mean of evaluating sweating levels. Both qualitative and quantitative techniques have been used to measure sweating levels. For example, qualitative measurements include iodine starch method and Minor's method, whereas weight measurement and ventilation capsule method are used as quantitative measurements (*11,12*). Each of these techniques is either time-consuming or it restricts the subject's physical activity by the firmly-attached measurement probes. Capillaroscopy, meanwhile, is readily and commonly used for the observation of capillary abnormalities in SSc patients, and has the advantage of being a brief and real-time quantification of sweat secretion by use of a small probe. We were able to prove its reproducibility, and our method can be considered as a new option for evaluation of sweat ability.

Second, contrary to expectation, we found patients with typical SSc that fulfilled ACR/EULAR 2013 classification criteria have significantly increased finger sweating levels compared with patients in pre-clinical stage of SSc that did not meet the classification criteria. Considering that the SSc patient group with high sweating levels tended to have a shorter disease duration, there is a possibility that serial measurement of finger sweating levels may help early differentiation of typical SSc from pre-clinical stage of SSc.

Another finding of this study is that, among patients with typical SSc, the ratio of dcSSc was significantly higher in patients with increased sweating levels compared to those with the normal sweating levels. The increased positivity of topoisomerase I antibody in patients with increased sweating levels supported this notion. As described above, sweating of SSc patients has been believed to be impaired because collagen accumulation causes atrophy of the sweat glands. Our unexpected results suggest the possibility that sweating is regulated by the autonomic nervous system (*13,14*), and it may be stimulated for unknown reasons in SSc patients. Alternatively, because skin sclerosis of the finger pads is usually mild, there may be compensatory hyperhidrosis. To prove this hypothesis, the sweating levels of other sites including sclerotic lesions using the same method by capillaroscopy are needed. In our preliminary data, however, we could not obtain reproducible results in sclerotic lesions (data not shown).

The current study has several limitations. First, we did not compare the results on sweating levels detected by the video capillaroscopy to those by any standard methods (*e.g.* iodine-starch test and/or perspiration meter). There are the possibility that the difference of sweating secretion ability among patient groups become clearer by the forced sweating situation such as warm. Next, the data of age/sex-matched healthy subjects was not available, because they rarely visit our hospital as a center in the area. Thus, we could not compare sweating levels of SSc patients with those of healthy control. In addition, the result from healthy subjects was very variable. Although we tried to identify the factor that influenced to sweat secreting, it is still unknown. Furthermore, 13.2% of Japanese SSc patients are reported to accompanied with Sjögren's syndrome (*15*). Because only one typical SSc had been diagnosed with Sjögren's syndrome in this study, ruling out of Sjögren's syndrome might not be enough in some patients. Even if some SSc patients are accompanied with Sjögren's syndrome, however, this does not explain increased sweating levels in typical SSc. Lastly, we did not record skin score and nailfold capillary findings, and these data was not available. The relationship between the clinical disease course (*e.g.* by the changes of skin score) and the changes of finger sweating levels could not be clarified in this manuscript. We will deal with these problems in the future project.

In summary, this pilot study indicated that measurement of finger sweating levels has potential usefulness for early diagnosis and clarification of pathogenesis in SSc. Detailed research with larger number of samples is necessary to prove its usefulness.

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