An evaluation of the efficacy of the toe brachial index measuring vascular involvement in systemic sclerosis and other connective tissue diseases

Y. Muro, K. Sugiura, Y. Morita, Y. Tomita

Division of Connective Tissue Disease and Autoimmunity, Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Yoshinao Muro, MD, PhD
Kazumitsu Sugiura, MD, PhD
Yukiko Morita, MD, PhD
Yasushi Tomita, MD, PhD

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Please address correspondence and reprint requests to:
Yoshinao Muro, MD, PhD,
Department of Dermatology,
Nagoya University Graduate School of Medicine, 65 Turumai-cho Showa-ku,
Nagoya, 466-8550, Japan.
E-mail: ymuro@med.nagoya-u.ac.jp

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ABSTRACT

Objective. *The ankle and toe brachial indices (ABI and TBI) are calculated as the ankle and toe systolic blood pressures divided by the highest brachial systolic pressure, respectively. We sought to evaluate the efficacy of ABI and TBI as an objective, non-invasive assessment of vascular involvement in patients with systemic sclerosis (SSc) and to investigate the clinical significance of TBI in SSc.*

Methods. *ABI and TBI were measured using an oscillometric method in 136 outpatients, including 77 with SSc, 29 with systemic lupus erythematosus (SLE), 16 with primary Sjögren's syndrome (SjS), and 14 with dermatomyositis (DM). We also analyzed 21 healthy controls.*

Results. *The mean ABI and frequency of reduced ABI values (<1.0) did not differ significantly between disease groups. TBI values in patients with SSc and lSSc were significantly lower than in those with SjS and DM, respectively ($p<0.01$). Patients with SSc and lSSc had significantly lower TBI values than healthy controls ($p<0.05$). Reduced TBI values (<0.6) were significantly more common in patients with SSc, including both dSSc and lSSc, than in those with SLE ($p<0.05$). Similarly, the frequency of decreased TBI was higher in patients with SSc and dSSc than in those with SjS or healthy controls ($p<0.05$). Skin ulcers ($p=0.041$) or overlap with rheumatoid arthritis ($p=0.018$) were associated with reduced TBI values by logistic regression analysis.*

Conclusion. *The TBI value is a useful, non-invasive tool to evaluate vascular involvement in SSc.*

Introduction

Systemic sclerosis (SSc) is characterized by thickening of the skin, fibrotic changes in the joints, muscles, and visceral organs, abnormalities in the microcirculation, and autoimmunity (1). Patients with SSc display diverse clinical courses with a broad spectrum of involved organs and severity. Vascular abnormalities, including Raynaud's phenomenon, digital pitting ulcers, and digital gangrene, are frequently seen in patients with SSc. Although these involvements rarely predict mortality in SSc patients (2), they are often assessed as indicators of the SSc-specific quality of life (3). As the evaluation of vascular disorders in patients with SSc currently relies on a physical examination, an objective and non-invasive assessment of arterial supply is needed.

The ankle brachial index (ABI) measures the status of large and small arteries in the lower extremity. The ABI for each leg is calculated separately by dividing ankle systolic pressure in that leg by the higher brachial systolic pressure (4). If arterial blood flow is normal, pressure at the ankle should be equal or slightly higher than that in the arm, resulting in an ABI ratio of > 1.0 (5). ABI measurement has a 90% sensitivity and 95% specificity for the detection of peripheral vascular disease (PVD) (6).

Toe pressure, which reflects arterial obstruction proximal to the digits, does not appear to be affected by arterial incompressibility. The ankle-to-toe pressure difference is increased in the majority of patients with PVD (7). For patients with rigid ankle blood vessels, toe pressure measurements should be taken as toe arteries are rarely rigid (8). A toe brachial index (TBI) is calculated from the systolic blood pressures of the arm and toes. For example, a subset of diabetics and patients on dialysis who develop varying degrees of calcification in lower limb arteries exhibit artifactually high ankle systolic pressures (9, 10). As arterial calcification is greater

at the ankles than at the toes, measurement of TBI is advocated in diabetic or dialyzed patients. Although the level defining ischemia has not been standardized, several investigators have reported that a TBI <0.64 is associated with arterial insufficiency (7, 11).

This study is the first to evaluate the efficacy of the ABI and TBI in assessing vascular involvement mainly in patients with SSc versus other connective tissue diseases. We also investigated the clinical significance of TBI measurement in an objective assessment of vascular involvement in SSc patients.

Table I. Patient profiles.

Disease	Number	Sex	Age	
		male : female	yrs	mean ± standard deviation
SSc	77	5 : 72	19 – 83	62 ± 11
dSSc	22	3 : 19	38 – 77	60 ± 11
lSSc	55	2 : 53	19 – 83	62 ± 11
SLE	29	0 : 29	37 – 80	57 ± 11
SjS	16	0 : 16	39 – 73	59 ± 9.9
DM	14	2 : 12	33 – 70	57 ± 8.8
Healthy controls	21	1 : 20	39 – 83	61 ± 11

SSc: systemic sclerosis; dSSc: diffuse cutaneous SSc; lSSc: limited cutaneous SSc; SLE: systemic lupus erythematosus; SjS: Sjögren syndrome; DM: dermatomyositis.

Materials and methods

Patients and controls

All patients examined in the study were followed by the Department of Dermatology at Nagoya University Hospital. The patients enrolled in this study were consecutive outpatients, and patients under 18 years old were excluded from the study. Of the 136 outpatients, comprised of 77 with SSc, 29 with systemic lupus erythematosus (SLE), 16 with primary Sjögren syndrome (SjS), and 14 with dermatomyositis (DM), 129 were female and 7 were male, with ages ranging from 19 to 83 years and a mean age of 60 years (Table I). All SSc patients fulfilled a new Japanese criterion, modified from the American College of Rheumatology (ACR) criteria (12), proposing a diagnosis of SSc with either the major criterion of proximal scleroderma or the minor criteria of sclerodactyly with one or more of the following: 1) digital pitting scars on the fingertips or loss of substance of the distal finger pads, 2) bilateral basilar pulmonary fibrosis, or 3) positive anti-Scl-70 or anti-centromere antibodies. According to the classification system of Leroy *et al*. (13), 22 patients exhibited diffuse cutaneous SSc (dSSc), while 55 had limited cutaneous SSc (lSSc). Six patients with SSc exhibited overlapping rheumatoid arthritis (RA) according to the ACR criteria (14). All SLE patients fulfilled ACR criteria (15). SjS was diagnosed according to Japanese criteria (16). Patients were diagnosed with DM according to the diagnostic criteria proposed by Bohan and Peter (17, 18); two definite, nine probable, and three possible cases were included. Normal control subjects (n=21) were identified from the age/sex-matched register of the general community or staff members. These individuals had no history of connective tissue disease.

Written informed consent was obtained from each subject. This study was approved by the local Ethical Committee.

Clinical assessment

Clinical features were obtained at the time when blood pressures were measured. As for organ involvement, patients were evaluated for the presence of pulmonary, esophageal, cardiac, renal, and muscular involvement. A value greater than one on the Japanese SSc severity scale (19), modified from Medsger's severity scale (20), was defined as the presence of organ involvement. Briefly, pulmonary fibrosis was diagnosed by radiographical findings of bibasilar interstitial fibrosis. We considered patients to have pulmonary hypertension based on increased pulmonary arterial systolic pressure (>25mmHg) that was estimated from an echocardiogram. Cardiac involvement included a conduction defect on electrocardiogram or left ventricular congestive heart failure (left ventricular ejection fraction <50%). Renal involvement was determined from a history of scleroderma renal crisis with increased serum creatinine level (>0.9 mg/dl). As the Japanese scale does not include muscular manifestations, we defined muscle involvement as mild proximal muscle weakness with elevated serum creatine kinase level according to Medsger's severity scale (20). Patients with GERD-like symptoms, such as heartburn and/or acid regurgitation, were diagnosed with esophageal involvement. Among the risk factors for atherosclerosis, a history of smoking, hypertension, hyperlipidemia, and diabetes mellitus were assessed. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. Hyperlipidemia was diagnosed based on elevated total cholesterol levels (≥220 mg/dl) or serum triglyceride levels (≥150 mg/dl). Patients with fasting plasma glucose ≥126 mg/dl were diagnosed with diabetes mellitus.

Measurement of arterial pressures

The brachial, ankle, and toe arterial pressures were measured between August 2006 and August 2007 by an oscillometric method using a waveform analyzer, form PWV/ABI® (OMRON HEALTHCARE Co. Ltd, Kyoto, Japan). The authors have no conflicts of interest with the manufacturer of this analyzer. Room temperature was maintained between 22 and 26°C. The ABI and TBI were calculated as the highest ankle and toe systolic pressures divided by the highest brachial systolic pressure, respectively. These index values were analyzed by the means of right and left values. ABI values <1.0 and TBI values <0.6 denoted the presence of PVD. For cases whose toe arterial pressure could not be measured because of poor circulation, we tentatively designated the unmeasurable values as 0.5, which was higher than the expected value since the minimum value of unilateral TBI was 0.30. When

Table II. Ankle brachial index and toe brachial index for various disease groups and healthy controls.

Disease	ABI		TBI	
	mean	reduction rate (%)[#]	mean	reduction rate (%)[#]
SSc	1.10	7/77 (9.1)	0.68[*]	20/77 (26)[**]
dSSc	1.11	2/22 (9.1)	0.70	8/22 (36)[**]
lSSc	1.10	5/55 (9.1)	0.68[*]	12/55 (22)[**]
SLE	1.08	3/29 (10)	0.73	1/29 (3.4)
SjS	1.11	0/16 (0)	0.81	0/16 (0)
DM	1.09	1/14 (7.1)	0.80	1/14 (7.1)
Healthy controls	1.09	1/21 (4.8)	0.75[§]	1/21 (4.8)

SSc: systemic sclerosis; dSSc: diffuse cutaneous SSc; lSSc: limited cutaneous SSc; SLE: systemic lupus erythematosus; SjS: Sjögren syndrome; DM: dermatomyositis; ABI: ankle brachial index; TBI: toe brachial index. [#]Reduction rate reveals the proportion of ABI values <1.0 and TBI values <0.6 in individual patient groups. [*]$p<0.01$ in SSc *vs*. DM, SSc *vs*. SjS, lSSc *vs*. DM, and lSSc *vs*. SjS with ANOVA (Bonferroni test). [**]$p<0.05$ in SSc *vs*. SLE, SSc *vs*. SjS, SSc *vs*. Control, dSSc *vs*. SLE, dSSc *vs*. SjS, dSSc *vs*. Control, and lSSc vs. SLE by chi-squared test. [§]$p<0.05$ in SSc vs. Control and lSSc *vs*. Control by the unpaired Student's t-test.

ABI/TBI were measured more than once within the duration of the study, we analyzed the first value only.

Statistical analysis

The normality and homogeneity of variance were confirmed in the data analysis. The indices (ABI/TBI) of disease groups were compared by ANOVA (Bonferroni test). Student's *t*-tests (two-tailed, unpaired) were performed to compare index values between SSc patients and the control group and to compare the means of reduced and normal TBI groups. Chi-squared tests were used to compare ABI/TBI reduction rates between groups and to assess the association between TBI reduction rates and each clinical parameter. A logistic regression analysis was used to identify parameters independently associated with reductions in TBI by a stepwise procedure that stopped when all variables obtained a value of $p<0.05$. Age, gender, and disease duration were forced into the model for adjustments. Statistical procedures were performed using SPSS Ver.15 statistical software from SPSS Japan, Inc. A *p*-value less than 0.05 was considered to be statistically significant.

Results

Clinical features of vascular manifestations

Among 77 patients with SSc, 54 patients had Raynaud's phenomenon, which was determined based on the patient's subjective complaints. Digital ulcers, ulcers in other areas, and digital gangrene were found in 15, 2 (1 at the elbow, 1 at the sole), and 3 patients, respectively. A total of 18 patients with SSc had a skin ulcer and/or gangrene. Twenty, 39, 13, 2, and 3 patients were classified into grade 0 (no Raynaud's phenomenon), grade 1 (Raynaud's phenomenon), grade 2 (digital ulcers), grade 3 (ulcers in other areas), or grade 4 (gangrene), respectively, based on the severity of vascular involvement according to the Japanese SSc severity scale (19). None of the patients with connective tissue diseases other than SSc had skin ulcers or gangrene. Raynaud's phenomenon was present in 9, 3, and 2 patients with SLE, SjS, and DM, respectively.

As for the pharmacological treatment of vascular disorders at the time of evaluation, anti-platelet drugs were used in 21, 13, 2, and 2 patients with SSc, SLE, SjS, and DM, respectively. Oral prostaglandines were administered to 33, 3, 0, and 2 patients with SSc, SLE, SjS, and DM, respectively ($p<0.001$ for SSc vs. SLE, SjS). Calcium antagonists were given to 4, 1, 2, and 2 patients with SSc, SLE, SjS, and DM, respectively. Vitamin E was also administered to 46, 10, 2, and 2 patients with SSc, SLE, SjS, and DM, respectively ($p<0.029$ for SSc *vs*. SLE, $p<0.01$ for SSc *vs*. DM, $p<0.001$ for SSc *vs*. SjS). No healthy controls were administered these medications.

Some patients were examined for the presence of anti-phospholipid antibodies. None of 14 dSSc patients and three of 28 lSSc patients had at least one of the following antibodies: lupus anticoagulants, anti-β2-glycoprotein I, and anti-cardiolipin. Nine of 26 patients with SLE had at least one of these antibodies ($p<0.01$ for SLE *vs*. SSc). Seven SjS patients and three DM patients did not have any of these antibodies.

ABI and TBI values of disease groups

We measured the mean values and reduction rates of ABI/TBI in all groups (Table II). Comparison of the mean values by ANOVA revealed that ABI values did not differ significantly between disease groups. While there were no significant differences in TBI values between the subset of patients with dSSc and those with other diseases, TBI values seen in SSc and lSSc patients were significantly lower than those seen in patients with SjS and DM, ($p<0.01$). Patients with SSc and lSSc had significantly lower TBI values than healthy controls ($p<0.05$) by the unpaired Student's *t*-tests. Toe arterial pressure could not be measured in seven cases, including two patients wtih dSSc, four with lSSc, and one with SLE. Two patients with dSSc, two with lSSc, and one with SLE exhibited unmeasurable unilateral pressures, while two patients with lSSc had unmeasurable pressures bilaterally. Although TBI values for the unmeasurable sites were defined as 0.5 in this analysis, the statistical results were similar if these values were set at 0.3 or 0.4 (data not shown).

Using the chi-squared test, we explored the proportion of patients with reduced indices of ABI values <1.0 and TBI values<0.6. There were no significant differences in the frequency of reduced ABI values between the disease groups. The proportion of patients with reduced TBI values was significantly greater in SSc, including dSSc and lSSc, than in SLE ($p<0.05$). The frequency of decreased TBI was similarly greater in SSc and dSSc patients than in those with SjS or healthy control ($p<0.05$).

Fig. 1 represents ABI (A) and TBI (B) values as evaluated in patients with a variety of diseases using box-and-whisker plots. One patient with dSSc exhibited outlying TBI values (= 1.2).

Correlation of the TBI reduction with clinical features and organ involvements in SSc

We summarized the clinical features and organ involvements seen for SSc patients with reduced TBI values (less than 0.6) and normal values (more than 0.6) (Table III). There were no significant differences between the two groups in age, gender, disease duration, smoking history, the presence of hyperlipidemia or diabetes, and the daily dosage of prednisolone. By univariate analysis, patients with reduced TBI values had an increased frequency of overlapping RA than those with normal TBI values (20% vs. 3.5%, p=0.04). Hypertension was more frequently seen in the normal TBI group than in the reduced TBI group (30% vs. 5%, p=0.03). Logistic regression analysis demonstrated that overlapping rheumatoid arthritis [Odds ratio (OR): 13.5; 95% confidence interval (CI): 1.56-118; p=0.018] and the presence of a skin ulcer/gangrene (OR: 4.48; 95% CI: 1.06-18.9; p=0.041) were all independently associated with a reduction in TBI. Two patients with grade 0, 10 with grade 1, 7 with grade 2, 1 with grade 3, and 0 with grade 4 had a low TBI. By the Mann-Whitney U-test, the severity of vascular involvement was also associated with reduced TBI values (p<0.026). We did not observe any significant associations between reduced TBI values and the presence of autoantibodies, such as anti-topoisomerase I or anti-centromere antibodies (data not shown). Similar analyses we performed for reductions in ABI values, however, did not reveal any significant correlation between ABI reduction and clinical features or organ involvements in disease (data not shown).

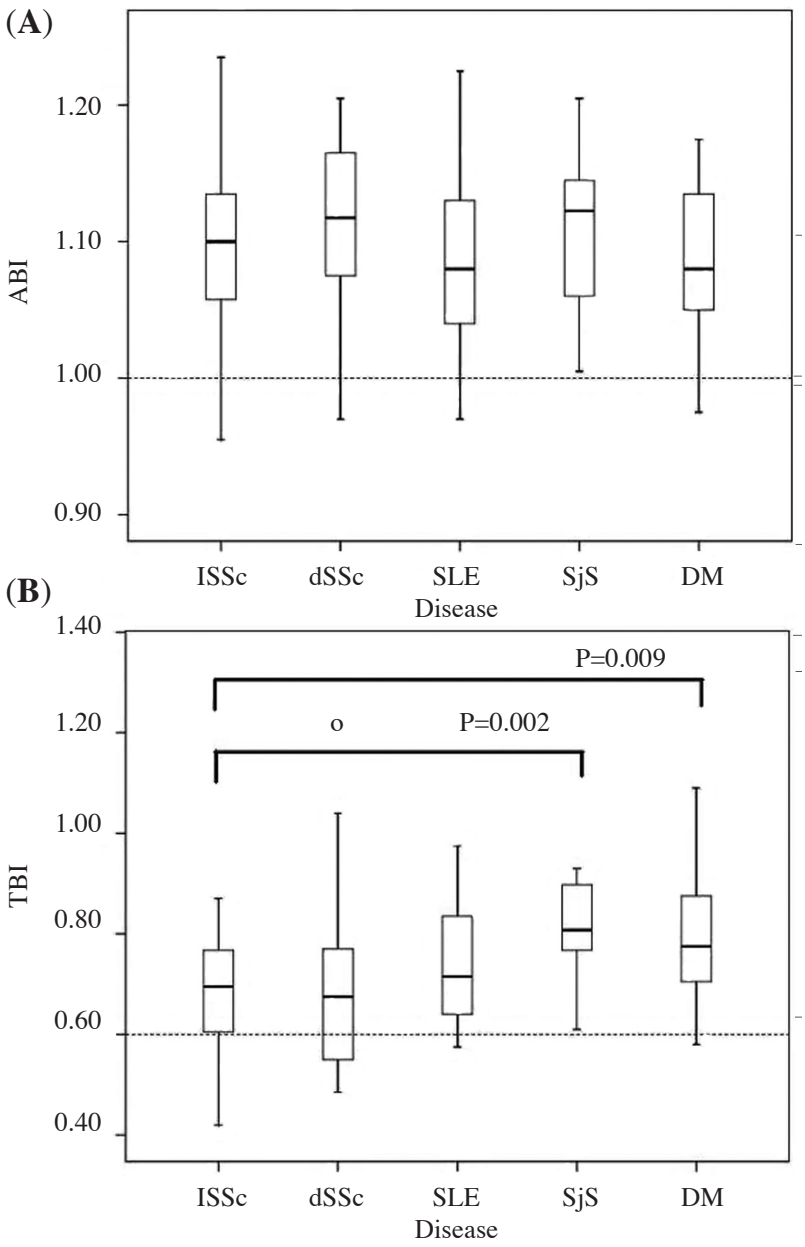

Fig. 1. Box-and-whisker plots displaying ABI (**A**) and TBI (**B**) values for disease groups. The central lines indicate medians of the data with the surrounding boxes extending to the lower and upper quartiles. The whiskers extend to the range of the data with the outlier, indicated by open circles. The horizontal dotted lines represent an ABI of 1.0 (**A**) and a TBI of 0.6 (**B**). Comparisons between disease groups were made using ANOVA (Bonferroni test). *P*-values less than 0.05 were considered to be significant.
SSc: systemic sclerosis; dSSc: diffuse cutaneous SSc; lSSc, limited cutaneous SSc; SLE: systemic lupus erythematosus; SjS: Sjögren syndrome; DM: dermatomyositis.

Discussion

Patients with SSc frequently display vascular involvement, which manifests as Raynaud's phenomenon, digital pitting ulcers, and digital gangrene. Although thermography has been used to assess vascular involvement in patients with SSc, this procedure is cumbersome (21). To evaluate vascular involvement in SSc, simple, objective, and noninvasive methods are necessary, which could facilitate early detection and treatment of the disorder.

In this study, we evaluated the efficacy of ABI and TBI measurements in the management of vascular involvement in SSc patients. For this study, our definition of the ABI cut-off value as 1.0 was supported by the fact that no patient exhibited a value <0.90, which the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) II Working Group defined as an abnormal ABI (22). According to the manufacturer's instructions, an ABI level <0.9 is defined

Table III. Correlation of TBI reductions with clinical features and organ involvements in patients with systemic sclerosis.

	TBI		Univariate*	Multivariate#	
	Reduced (<0.6) (%) n=20	Normal (%) n=57	*p*	*p*	Odds ratio (95% CI)
Age (mean years)	61	62	0.78	0.81	1.01 (0.95-1.07)
Gender (M: F)	1:19	4:53	1.00	0.50	2.69 (0.15-47.3)
Disease duration (mean years)	15	11	0.12	0.09	1.06 (0.99-1.12)
PSL (mg/day, mean dosage)	2.6	2.1	0.58		
Smoking	4 (20)	11 (19)	1.00		
Hypertension	1 (5)	17 (30)	**0.03**	**0.028**	0.07 (0.01-0.75)
Hyperlipidemia	3 (15)	14 (25)	0.44		
Diabetes	2 (10)	6 (11)	1.00		
Overlap of RA	4 (20)	2 (3.5)	**0.04**	**0.018**	13.5 1.56-118)
Clinical features					
mRss (mean)	5.9	6	0.93		
skin ulcer/gangrene	8 (40)	10 (18)	0.06	**0.041**	4.48 (1.06-18.9)
Nailfold bleeding	11 (55)	32 (56)	1.00		
Raynaud's Ph.	16 (80)	38 (67)	0.40		
Telangiectasia	13 (65)	34 (60)	0.79		
Calcinosis	4 (20)	7 (12)	0.46		
Sicca symptoms	13 (65)	36 (63)	1.00		
Arthralgia	12 (60)	25 (44)	0.30		
Organ involvements					
Pulmonary fibrosis	10 (50)	23 (40)	0.66		
Pulmonary hypertension	2 (10)	4 (7.0)	0.69		
Oesophagous	12 (60)	31 (54)	0.78		
Heart	4 (20)	4 (7.0)	0.26		
Kidney	1 (5)	2 (3.5)	1.00		
Muscle	2 (10)	4 (7.0)	0.89		

PSL: prednisolone; RA: rheumatoid arthritis; mRss: modified Rodnan skin score; 95% CI: 95% confidence interval.

*The comparison of means between reduced and normal TBI groups was performed using the Student's *t*-test (two-tailed, unpaired). Chi-squared tests were used to assess the association between the proportion of reduced TBI values and each clinical parameter.

#Logistic regression analysis was performed to identify parameters independently associated with reductions in TBI using a stepwise procedure. Only variables with $p<0.05$ remained. Age, gender, and disease duration were forced into the model for adjustments.

as abnormal and 0.9~1.0 as borderline abnormal. Although the normal range for TBI has not been strictly defined (7, 11), several investigators have reported TBI cut-off values ranging from 0.5 to 0.7 (23, 24). In this study, we considered TBI values <0.60 as abnormal based on the manufacturer's instructions. Our results demonstrated that TBI values were significantly lower in patients with SSc (mean value: 0.68). The proportion of patients with reduced TBI values was also significantly higher (the reduction rate: 26%) in SSc than in other connective tissue diseases or healthy controls. Using a logistic regression analysis, we determined that a skin ulcer was independently associated with reduced TBI values. The analysis in SSc patients, even those lacking overlapping RA, revealed similar results (data not shown). Our results demonstrated that TBI measurement is a useful technique for evaluating vascular disorders in SSc.

Although the proportion of patients with dSSc exhibiting reduced TBI values was significantly greater (the reduction rate: 36%) than those with other connective tissue diseases, we did not observe a significant difference in the average TBI value between patients with dSSc and other diseases. This result was attributable to the outlying TBI value seen in one patient with dSSc. Indeed, ANOVA performed when excluding this patient revealed that TBI values seen in dSSc patients were significantly lower than those seen in patients with SjS and DM ($p<0.05$, data not shown). Although toe pressures are rarely affected by arterial calcification (10), TBI may occasionally provide falsely elevated values in patients with processed arteriosclerosis reflecting arterial calcification. The dSSc patient with the outlying TBI value also carried a ten-year diagnosis of diabetes mellitus, which may have been associated with processed arteriosclerosis.

Logistic regression analysis revealed that the presence of overlapping RA was independently associated with reduced TBI values. A subset of SSc cases exhibit clinical characteristics of RA, dubbed overlap syndrome (SSc-RA) (25, 26); these patients exhibit more severe arthralgias and functional impairment than patients with SSc alone (27). Previous investigations utilizing the Health Assessment Questionnaire (HAQ) clarified that patients suffering from SSc-RA exhibit greater functional impairments than patients with SSc alone, as evidenced by a higher HAQ-disability index (HAQ-DI) (28, our unpublished observations). Poor blood flow, which could be assessed as consequent reductions in TBI, may underlie this functional impairment in SSc-RA. Future investigations are needed to clarify the association between reductions in TBI and HAQ-DI or scleroderma HAQ (29).

In a recent study, Kido, *et al*. reported the efficacy of a microwireless laser doppler flowmeter for assessing abnormal blood flow in eight patients with SSc (30). Although this tool is useful, it requires a provocation method, such as cold provocation and the arm-raising test. In this regard, TBI measurements do not require a provocative test and the values are automatically calculated. Since our method is easily applied for clinical use, many patients can be evaluated in a short time. Furthermore, the waveform analyzer used in this study can coincidentally measure pulse wave velocity (PWV), which is an indicator of the presence and degree of arterial stiffening. Very recently, Timár *et al*. revealed that PWV in SSc patients was significantly higher than in age- and

sex-matched healthy controls (31). Although increased vascular stiffness in SSc patients may be associated with vascular function, we did not see an association between PWV and SSc (data not shown).

In conclusion, the assessment of TBI is preferable to ABI in evaluating vascular involvement in patients with SSc. It may be possible to use TBI, which is an objective and non-invasive marker, for both the determination of therapeutic efficacy and drug discovery in the future. Additional studies are needed to further confirm the usefulness of TBI, including longitudinal studies that follow SSc patients with vascular involvement for long periods.

References

1. TUFFANELLI DL, WINKELMANN RK: Systemic scleroderma: a clinical study of 727 cases. *Arch Dermatol* 1961; 84: 359-71.
2. KARASSA FB, IOANNIDIS JPA: Mortality in systemic sclerosis. *Clin Exp Rheumatol* 2008; 26: S85-93.
3. VALENTINI G, CERINIC M: Disease-specific quality indicators, guidelines and outcome measures in scleroderma. *Clin Exp Rheumatol* 2007; 25: S159-62.
4. HIRSCH AT, CRIQUI MH, TREAT-JACOBSON D *et al*.: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; 286: 1317-24.
5. STOFFERS J, KAISER V, KESTER A, SCHOUTEN H, KNOTTNERUS A: Peripheral arterial occlusive disease in general practice: the reproducibility of the ankle-arm systolic pressure ratio. *Scand J Prim Health Care* 1991; 9: 109-14.
6. CRIQUI MH: Systemic atherosclerosis risk and the mandate for intervention in atherosclerotic peripheral arterial disease. *Am J Cardiol* 2001; 88: 43J-47J.
7. CARTER SA, LEZACK JD: Digital systolic pressures in the lower limb in arterial disease. *Circulation* 1971; 43: 905-14.
8. ORCHARD TJ, STRANDNESS DE JR: Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Diabetes Association and the American Heart Association. *Circulation* 1993; 88: 819-28.
9. MAYFIELD JA, REIBER GF, SANDERS LJ, JANISSE D, POGACH LM: Preventive foot care in people with diabetes. *Diabetes Care* 1998; 21: 2161-79.
10. YOUNG MJ, ADAMS JE, ANDERSON GF, BOULTON AJM, CAVANAGH PR: Medical arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia* 1993; 36: 615-21.
11. LEZACK JD, CARTER SA: The relationship of distal systolic pressures to the clinical and angiographic findings in limbs with arterial occlusive disease. *Scand J Clin Lab Invest* 1973; 31 (Suppl. 128): 97-101.
12. SUBCOMMITTEE FOR SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
13. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
14. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
15. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
16. FUJITA M, IGARASHI T, KURAI T, SAKANE M, YOSHINO S, TAKAHASHI H: Correlation between dry eye and rheumatoid arthritis activity. *Am J Ophthalmol* 2005; 140: 808-13.
17. BOHAN A, PETER JB: Polymyositis and dermatomyositis (first of two parts). *N Eng J Med* 1975; 292: 344-7.
18. BOHAN A, PETER JB: Polymyositis and dermatomyositis (second of two parts). *N Eng J Med* 1975; 292: 403-7.
19. TAKEHARA K, SATO S: The clarification of pathogenesis and the development of therapy in systemic sclerosis: the classification of severity and the guideline for treatment (2007). Edited by, a research project for systemic sclerosis supported by Japanese Ministry of Health and Welfare; 2007.
20. MEDSGER TA JR, BOMBARDIERI S, CZIRJAK L, SCORZA R, DELLA ROSSA A, BENCIVELLI W: Assessment of disease severity and prognosis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 29): S42-6.
21. ANDERSON ME, MOORE TL, LUNT M, HERRICK AL: The 'distal-dorsal difference': a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. *Rheumatology* (Oxford) 2007; 46: 533-8.
22. NORGREN L, HIATT WR, DORMANDY JA, NEHLER MR, HARRIS KA, FOWKES FG: TASC II Working Group: Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45 (Suppl. S): S5-67.
23. BONHAM PA: Get the LEAD out: noninvasive assessment for lower extremity arterial disease using ankle brachial index and toe brachial index measurements. *J Wound Ostomy Continence Nurs* 2006; 33: 30-41.
24. CRITICAL LEG ISCHAEMIA PREVENTION STUDY (CLIPS) GROUP, CATALANO M, BORN G, PETO R: Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *J Intern Med* 2007; 261: 276-84.
25. ZIMMERMANN C, STEINER G, SKRINER K, HASSFELD W, PETERA P, SMOLEN JS: The concurrence of rheumatoid arthritis and limited systemic sclerosis: clinical and serologic characteristics of an overlap syndrome. *Arthritis Rheum* 1998; 41: 1938-45.
26. MORITA Y, MURO Y, SUGIURA K, TOMITA Y: Anti-cyclic citrullinated peptide antibody in systemic sclerosis. *Clin Exp Rheumatol* 2008; 26: 542-7.
27. HORIKI T, MORIUCHI J, TAKAYA M *et al*.: The coexistence of systemic sclerosis and rheumatoid arthritis in five patients. Clinical and immunogenetic features suggest a distinct entity. *Arthritis Rheum* 1996; 39: 152-6.
28. MORITA Y, MURO Y, SUGIURA K, TOMITA Y, TAMAKOSHI K: Results of the Health Assessment Questionnaire for Japanese patients with systemic sclerosis – measuring functional impairment in systemic sclerosis versus other connective tissue diseases. *Clin Exp Rheumatol* 2007; 25: 367-72.
29. JOHNSON SR, HAWKER GA, DAVIS AM: The Health Assessment Questionnaire Disability Index and Scleroderma Health Assessment Questionnaire in scleroderma trials: an evaluation of their measurement properties. *Arthritis Rheum* 2005; 53: 256-62.
30. KIDO M, TAKEUCHI S, HAYASHIDA S, URABE K, SAWADA R, FURUE M: Assessment of abnormal blood flow and efficacy of treatment in patients with systemic sclerosis using a newly developed microwireless laser Doppler flowmeter and arm-raising test. *Br J Dermatol* 2007; 157: 690-7.
31. TIMÁR O, SOLTÉSZ P, SZAMOSI S *et al*.: Increased arterial stiffness as the marker of vascular involvement in systemic sclerosis. *J Rheumatol* 2008; 35: 1329-33.