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Myocardial Damages in Systemic Sclerosis Detected by Gated Myocardial Perfusion SPECT and Sympathetic Imaging

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Background Cardiac involvement is an important factor for the appropriate management of systemic sclerosis (SSc). The possibility for detecting early myocardial damage was investigated using ^{99m}Tc methoxyisobutylisonitrile (MIBI) gated perfusion single photon emission computed tomography (SPECT) and ^{123}I metaiodobenzylguanidine (MIBG) sympathetic imaging.

Methods and Results Twenty-three patients with SSc and 14 control subjects were studied. The severity of SSc was defined by disease type and semi-quantitative skin thickness scores. A myocardial perfusion study was performed using ^{99m}Tc MIBI exercise – rest study, and systolic and diastolic parameters were calculated from the volume curve of the gated SPECT. ^{123}I MIBG was evaluated by segmental defects, a heart-to-mediastinum ratio and washout rate (WR). No significant exercise-induced ischemia was observed and the left ventricular ejection fraction was within normal range in patients with SSc. However, diastolic function calculated by time to peak filling (TPF) in the early diastole was significantly prolonged in SSc compared with the control group (184±35 ms, 160±25 ms, p=0.030) and more rapid MIBG WR from the myocardium (18.2±7.0% vs 11.1±4.3%, p=0.0015). Compared with the control group, the severe group with either diffuse SSc or a skin thickness score ≥10 had more prolonged TPF/RR interval than the less severe group. Both diastolic and sympathetic abnormalities were observed in 7 (30%) patients, and 1 abnormality in 17 (74%) patients with SSc.

Conclusions In patients with SSc, either diastolic dysfunction or sympathetic derangement, or both were observed even without induced ischemia and normal ventricular contractility. Based on these subclinical early findings, further follow-up studies are recommended. (*Circ J* 2006; **70:** 1481 – 1487)

Key Words: Diastolic function; Gated SPECT; ^{123}I metaiodobenzylguanidine; Sympathetic imaging; Systemic sclerosis

In recent years, it has become evident that early diagnosis and accurate staging of visceral involvement are fundamental for appropriate management and treatment of systemic sclerosis (SSc)[1] Cardiac involvement in SSc can manifest as myocardial disease, pericardial disease, conduction system disease and arrhythmias, and is an important complication affecting the prognosis of SSc. In autopsy studies, myocardial involvement has been observed in as many as 20–50% of cases, which included a minor degree of abnormality[2,3] Of the noninvasive diagnostic tools, ^{201}Tl myocardial perfusion imaging has demonstrated a high incidence of stress- or cold-induced ischemia even without apparent clinical symptoms[4,5] and ^{99m}Tc myocardial perfusion imaging has also been used for the detection of abnormalities in systemic lupus erythematosus and SSc[6] However, few studies have evaluated its correlation to the types and severities of scleroderma. A study using myocardial gated perfusion single photon emission computed tomography (SPECT) has shown that the incidence of induced ischemia is relatively low, but that diastolic dysfunction may be an early sign of cardiac involvement[7] Another study showed the possibility of detecting myocardial abnormality using ^{123}I metaiodobenzylguanidine (MIBG) imaging in SSc, revealing that as many as 83% of patients had an MIBG abnormality[8] which was in accordance with the fact that MIBG imaging has been used as a sensitive marker for ischemia and myocardial damage. Thus, we hypothesized that early functional abnormalities would be detected using nuclear imaging with either perfusion or sympathetic imaging. The correlation to the severity of SSc was also investigated.

Methods

The study population consisted of 23 patients with SSc (54.1±11.7 years, 5 males, 18 females) and 14 control patients. The diagnosis of SSc was made in the Department of Dermatology based on American Rheumatism Association diagnostic criteria[9] The severity and involvement of organ lesions was determined using skin lesions and a general survey of the lungs, heart, kidney and digestive systems[9,10] Thirteen patients had diffuse cutaneous type SSc and 10 had limited type SSc. The total skin thickness score (TSS) based on modified Rodnan's criteria ranged from 1 to 38 (average 13.2±8.6, median 18)[11,12] Because our previous study in

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Table 1 ^{123}I MIBG and Gated SPECT Studies in the Control and Systemic Sclerosis Groups

	Control	Systemic sclerosis	p value
No. of patients	*14*	*23*	
Sex (M/F)	*4/10*	*5/18*	*NS*
Age (years)	*54.4±11.9*	*54.1±11.7*	*NS*
^{123}I MIBG			
Early heart/mediastinum ratio	*2.13±0.18*	*2.02±0.22*	*NS*
Delayed heart/mediastinum ratio	*2.31±0.16*	*2.04±0.29*	*0.0037*
Washout rate (%)	*11.1±4.3*	*18.2±7.0*	*0.0015*
Gated myocardial perfusion SPECT			
End-diastolic volume (ml)	*68.1±20.1*	*62.3±21.4*	*NS*
Ejection fraction (%)	*68.4±8.5*	*73.5±9.3*	*NS*
Peak filling rate (/s)	*2.55±0.55*	*2.76±0.66*	*NS*
Time to peak filling (ms)	*160.4±24.7*	*184.4±34.6*	*0.030*
Time to peak filling/RR interval	*0.179±0.029*	*0.214±0.056*	*0.039*

MIBG, metaiodobenzylguanidine; SPECT, single photon emission computed tomography.

patients with SSc showed significant diastolic abnormality in the diffuse type and those with TSS ≥10, we classified patients into 2 subgroups: severe (diffuse type or TSS ≥10) and mild (limited type and TSS <10). The threshold of TSS=10 was also in agreement with a report from the research project for SSc supported by the Japanese Ministry of Health and Welfare![13] Both MIBG and ^{99m}Tc methoxyisobutylisonitrile (MIBI) studies were performed in all patients. Control subjects were selected from low-risk patients in whom the possibility of ischemic heart disease was eliminated and who showed neither ECG nor echocardiography abnormalities, and did not have diabetes or hypertension. They were judged as having no major risk factors for coronary heart disease![14] The mean age was 54.1±11.7 years (4 males, 10 females), which did not differ significantly from that of the SSc group.

Myocardial Perfusion Study

The myocardial perfusion study was performed using a 1-day exercise–rest sequence protocol. Three patients could only undergo a resting study because of their poor condition. Approximately 300–370 MBq of ^{99m}Tc MIBI was injected at peak exercise with a multi-stage ergometer exercise. SPECT image acquisition was started after 30 min with a 64×64 matrix, 6-degree step and 360-degree rotation using a 3-detector system (Toshiba GCA 9300A, Tokyo, Japan). The data acquisition time was 60 s/projection and the total acquisition time was approximately 20 min. Low-energy parallel-hole collimators were used, and the energy was centered on 140 keV with a 20% window. A resting SPECT study was started 60 min after injection with 700–900 MBq. Gated SPECT was performed at rest with 16 frames per cardiac cycle and 60 s per projection. Although the RR acceptance window was set to 30%, no significant bad-beat rejection was recorded during the present study.

Myocardial perfusion was evaluated based on the standard 17-segment model with visual analysis. Quantification of gated SPECT was performed using QGS software (Cedars Sinai Medical Center, USA). After calculating the volume of each time-bin, Fourier fitting was performed with a direct current component to fourth harmonics. Volumes and ejection fraction (EF) were calculated using the standard algorithm of the QGS software. Diastolic parameters were calculated as peak filling rate (PFR) in the early diastole, time to peak filling (TPF) and TPF/RR interval. The TPF was defined as the time from end-systolic point to PFR. Mathematica 5.1 software (Wolfram Research, Inc, USA) was used for calculating dV/dt parameters.

^{123}I MIBG Study

^{123}I MIBG planar and SPECT studies were performed at 20 min (early) and 3 h (delayed) after injection with 111 MBq. The interval between MIBG and the perfusion studies was 3.9±2.4 days. In the planar study, a region of interest (ROI) was set over the heart and a rectangular ROI on the upper third of the mediastinum. The early and delayed heart-to-mediastinum average count ratios (H/M) were calculated, and the washout rate (WR) was calculated using the formula:

WR = (myocardial early count − delayed count)/early count after ^{123}I decay and background correction.

^{123}I MIBG SPECT study was performed with 64×64 matrix, 6-degree step and 360-degree rotation using a 3-detector SPECT system. The acquisition time was 60 s/projection. High-resolution, low-energy collimators were used, and the energy was centered on 159 keV with a 20% window. Myocardial MIBG defects and heterogeneity were analyzed visually by 2 nuclear medicine specialists.

Statistical Analysis

All the results are expressed as mean ± standard deviation (SD). The difference of the mean was tested using ANOVA. For comparisons among the 3 groups, a Dunnett test was performed. To compare the presence of abnormalities, contingency tables were made and a likelihood ratio and Pearson's chi-square tests were examined. Because TSS has an ordinal-scale nature, a non-parametric Spearman's rank-order correlation coefficient (rho) was also calculated. A p-value <0.05 was considered significant.

Results

When myocardial exercise-induced ischemia was examined, none of the SSc patients had a significant perfusion defect, although 3 patients showed a slight decrease in the apical inferior segment both at rest and during exercise. A slight area of hypoperfusion was seen in the inferior segment (n=1) and the apex (n=1) at rest. However, all of these findings were borderline and could not be judged as definite perfusion defects. No abnormal perfusion defect was observed in the control subjects.

Regarding the parameters of gated SPECT, EF was 73.5±9.3% and 68.4±8.5% for the SSc and control groups,

Table 2 Contingency Tables for Mild and Severe Groups of Systemic Sclerosis and Control Group

	Normal	Abnormal	Total	χ^2	p value
Abnormal TPF >200 ms					
Control	*14 (100%)*	*0 (0%)*	*14*		
Mild	*6 (86%)*	*1 (14%)*	*7*		
Severe	*9 (56%)*	*7 (44%)*	*16*		
Total	*29 (78%)*	*8 (22%)*	*37*		
Likelihood ratio				*10.962*	*0.0042*
Pearson				*8.707*	*0.0129*
Abnormal TPF/RR >0.23					
Control	*13 (93%)*	*1 (7%)*	*14*		
Mild	*7 (100%)*	*0 (0%)*	*7*		
Severe	*8 (50%)*	*8 (50%)*	*16*		
Total	*28 (76%)*	*9 (24%)*	*37*		
Likelihood ratio				*11.669*	*0.0029*
Pearson				*10.225*	*0.0060*
Abnormal delayed H/M ratio <2.00					
Control	*13 (93%)*	*1 (7%)*	*14*		
Mild	*4 (57%)*	*3 (43%)*	*7*		
Severe	*8 (50%)*	*8 (50%)*	*16*		
Total	*25 (68%)*	*12 (32%)*	*37*		
Likelihood ratio				*7.680*	*0.0215*
Pearson				*3.686*	*0.0353*
Abnormal MIBG washout rate >20%					
Control	*14 (100%)*	*0 (0%)*	*14*		
Mild	*5 (71%)*	*2 (29%)*	*7*		
Severe	*10 (63%)*	*6 (37%)*	*16*		
Total	*29 (78%)*	*8 (22%)*	*37*		
Likelihood ratio				*9.088*	*0.0106*
Pearson				*6.442*	*0.0399*

TPF, time to peak filling; H/M, heart-to-mediastinum average count ratios. Other abbreviation see in Table 1.

respectively (NS), and end-diastolic volume did not differ significantly between the 2 groups (Table 1). Regarding diastolic dysfunction, PFR did not differ significantly between the 2 groups, but TPF was significantly prolonged in the SSc group (184.4±34.6 ms) compared with the control group (160.4±24.7 ms) (p=0.030). TPF/RR also showed a significant difference between groups (0.214±0.056 vs 0.179±0.029, p=0.039).

A slight decrease in MIBG uptake was seen in 12 of 23 patients in the apical inferior region, but as this sort of decrease is often regarded as a non-specific finding, we did not judge it as an apparent abnormality. The MIBG distribution was judged as significantly heterogeneous in 3 patients. The early H/M ratio was 2.02±0.22 and 2.13±0.18 for the SSc and control groups, respectively (NS). The delayed H/M ratio was 2.04±0.29 and 2.31±0.16 for the SSc and control patients (p=0.0037), respectively. The WR was 18.2±7.0% and 11.1±4.3% for the SSc and control patients (p=0.0015), respectively. Thus, the patients with SSc had more delayed uptake and a more rapid MIBG clearance. No significant difference was observed between the diffuse and limited types with respect to diastolic function and MIBG parameters.

When we observed the relationship between TSS and MIBG parameters or diastolic parameters, Spearman's rank-order correlation coefficients (rho) were –0.43 between TSS and delayed MIBG H/M ratio (p=0.0078), 0.60 between TSS and MIBG WR (p=0.0013), 0.45 between TSS and TPF (p=0.0058), and 0.43 between TSS and TPF/RR (p=0.0072).

When the SSc patients were classified into the severe (n=17) and mild (n=6) subgroups, the mean age was 52.3±12.3 and 55.4±11.9 (NS), and TSS was 2.57±1.51 and 17.2±5.8 (p<0.0001) for the mild and severe groups. The TPF/RR was 0.189±0.024 and 0.225±0.062 for the mild and severe groups, respectively (p=0.029 by ANOVA, p=0.004 between the control and severe groups by Dunnett test). Regarding the MIBG study, delayed H/M was 2.12±0.22 and 2.04±0.37 for the mild and severe groups, respectively (p=0.047 by ANOVA, p=0.028 between the control and severe groups by Dunnett test). The MIBG WR showed 17.4±9.4% and 18.2±6.2% for the mild and severe groups, respectively (p=0.0106 for 3 groups by ANOVA, p=0.008 between the control and severe groups, and p=0.068 between the control and mild groups by Dunnett test).

Table 3 Incidence of Abnormal Findings for Diastolic Function and MIBG Parameters

	Normal	Abnormal			Total
		MIBG	Diastolic	Both	
Control	*11 (79%)*	*1 (7%)*	*1 (7%)*	*1 (7%)*	*14 (100%)*
SSc	*6 (26%)*	*6 (26%)*	*4 (17%)*	*7 (30%)*	*23 (100%)*

Likelihood ratio: χ^2=10.233, p=0.0167. Pearson: χ^2=9.728, p=0.0210. SSc, systemic sclerosis. Other abbreviation see in Table 1.

Table 2 shows the frequency of abnormality in the control, mild and severe groups. The contingency tables of abnormality are shown using the criteria of TPF >200 ms, TPF/RR >0.23, MIBG delayed H/M ratio <2.00 and MIBG WR >20% as abnormal values, which were determined using the 95% confidence interval for the mean of the control group. Regarding severity, the severe group had a significantly longer TPF and TPF/RR, and lower MIBG delayed H/M ratio and higher WR (Table 2). A fair positive correlation was observed between the MIBG WR and TPF/RR values (R=0.36, p=0.026). Table 3 shows the incidence of diastolic and sympathetic abnormalities in the control and

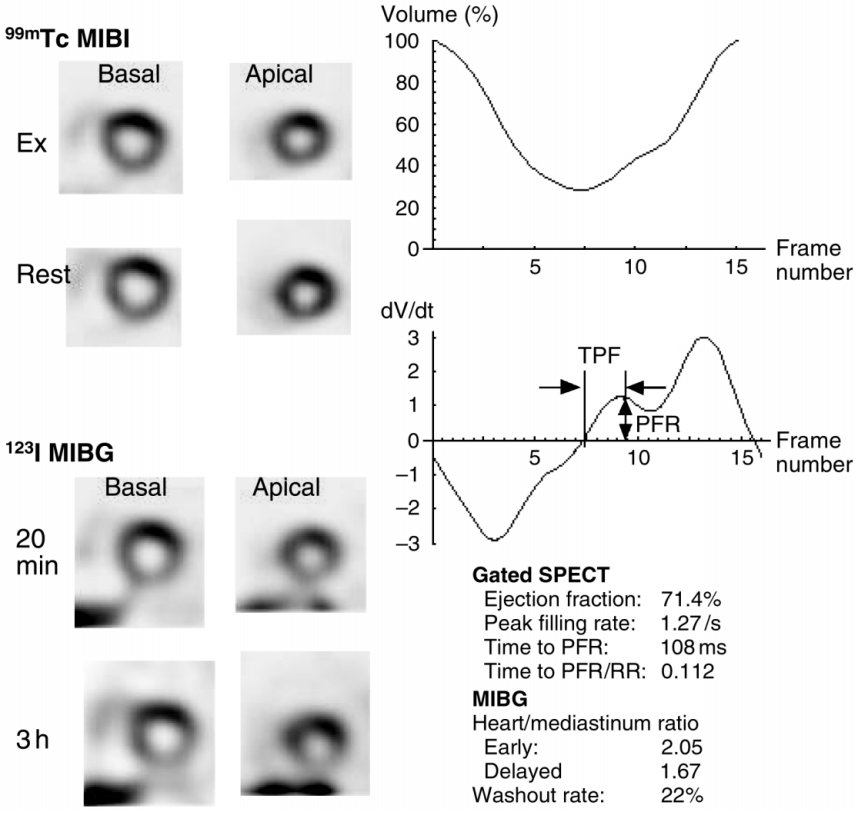

Fig 1. Patient with diffuse cutaneous-type systemic sclerosis (SSc) with total skin thickness score (TSS) 18, showing diastolic dysfunction. Basal and apical ^{99m}Tc methoxyisobutylisonitrile (MIBI) and ^{123}I metaiodobenzylguanidine (MIBG) slices are shown (Left). The volume curve and dV/dt curve showed diastolic dysfunction and MIBG parameters were also abnormal. Ex, exercise; TPF, time to peak filling; PFR, peak filling rate; SPECT, single photon emission computed tomography.

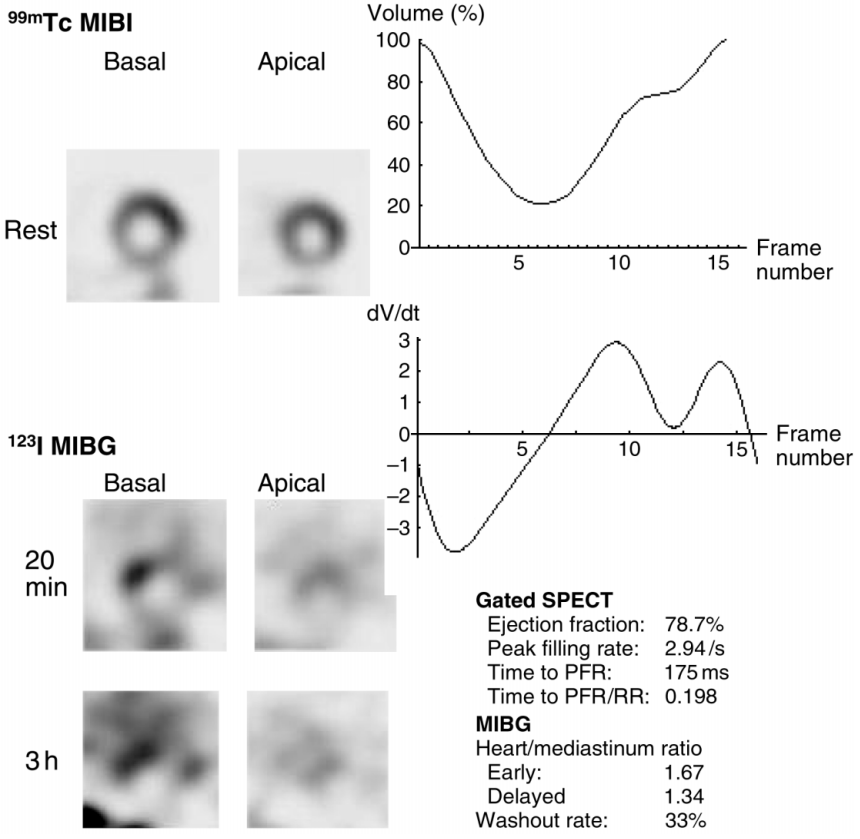

Fig 2. Patient with diffuse cutaneous-type systemic sclerosis with total skin thickness score 21, showing decreased metaiodobenzylguanidine (MIBG) activity and rapid washout rate. MIBG distribution showed marked heterogeneity in both early and delayed images. Resting perfusion and volume curve were normal. MIBI, methoxyisobutylisonitrile; SPECT, single photon emission computed tomography; PFR, peak filling rate.

SSc patients. Both abnormalities were observed in 7 (30%) and 1 of them in 17 (74%) of patients with SSc. The SSc patients showed significantly more frequent diastolic and sympathetic abnormalities than the control group (p=0.021).

The severe group recorded an ECG abnormality of ST-segment depression (n=1), supraventricular premature contraction (SVPC) (n=5), atrioventricular block (n=1), intraventricular conduction defect (n=1) and multiform premature ventricular contraction (n=2). Only sporadic SVPC (n=3) was observed in the mild type.

Fig 1 shows a 60-year-old female patient with diffuse cutaneous-type SSc. The duration from onset was 7 years. TSS was 18 (moderately high) and antibodies of both anti-topoisomerase I and anti-centromere were positive. Pulmonary function, vital capacity (%VC, 76%) and lung diffusion capacity for CO (%DLco, 31%) were decreased. The renal glomerular filtration rate was also decreased (27 ml/min). The myocardial perfusion study showed no abnormality at either peak exercise or at rest. However, gated SPECT showed significant diastolic dysfunction, represented by the decreased early filling dV/dt. In this patient, TPF was within normal limits, but PFR is low and compensatory augmentation of the atrial kick was evident, as shown by the second diastolic peak. ^{123}I MIBG showed decreased activity in the inferior walls. The delayed H/M ratio was decreased, and WR slightly increased. Fig 2 shows a 67-year-old female patient with diffuse cutaneous-type SSc. Her TSS was 21 and she had decreased diffuse lung capacity (%DLco, 50%) and glomerular filtration rate (56 ml/min). Although her gated perfusion study at rest was normal, MIBG showed heterogeneous activity and significantly decreased uptake.

Discussion

The major results of the present study are that patients with SSc have a high frequency of diastolic dysfunction and sympathetic abnormality as detected by myocardial perfusion gated SPECT and ^{123}I MIBG studies. Because perfusion abnormality was minimal in these patients, such findings may occur only in the early stage of cardiac dysfunction. SSc is a disease involving multiple organs and functional abnormalities, and thus the index for detecting the early stages of complication, therapeutic effect and prognosis has been considered important. Of these complications, cardiac functional abnormality is one of the most important prognostic factors, as well as lung and renal dysfunction. However, the diagnosis may be late or difficult because of frequent discrepancies between the clinical manifestation and real cardiac involvement. For this reason, to achieve an early diagnosis, using all the available diagnostic procedures is recommended!

According to previous studies using perfusion scans, ischemia and perfusion defects are frequently documented in patients with SSc[4,5] Follansbee showed that 20 of 26 patients had abnormal thallium scans, including 10 with reversible exercise-induced defects and 18 with fixed defects, and these conditions were attributed to a disturbance of the myocardial microcirculation[4] Another study found cold-induced reversible perfusion defects in 12 of 21 patients; 9 of them also had permanent defects![15] In 22 patients with collagen diseases, including SSc (n=13), 18 (82%) had abnormal findings on ^{201}Tl SPECT. Thes findings show that a myocardial perfusion study is an effective method of evaluating the wide spectrum of myocardial involvement in collagen disease![16] Studies using a ^{99m}Tc perfusion imaging agent have also shown a similar ability to detect ischemia as ^{201}Tl[6,17] A high frequency of perfusion abnormality (88%) in symptomatic patients is demonstrated compared with asymptomatic patients (38%) withn systemic lupus erythematosus and SSc. Compared with those studies, our study population had a relatively low incidence of myocardial ischemia as was also the case in another previous study[7]

Regarding the severity of SSc, few studies have evaluated the role of gated SPECT and sympathetic imaging. Although it is known that the diffuse cutaneous type has a higher incidence of myocardial complications, the diffuse type may be associated with less severe skin lesions. In contrast, the limited cutaneous type may have severe skin lesions. Because we found that the diffuse type, or TSS ≥10, had significant diastolic dysfunction, in the present study we defined severity based on the combination of both factors, and found significant differences between the groups. The use of TSS has been justified by its good correlation with organ involvement and good reproducibility, and it has been used as a reference for clinical trials![13,18,19] Therefore, a positive relationship to the TSS was meaningful in the present study.

The reason for the low incidence of stress-induced ischemia may be related to the severity of SSc in the present study population. In fact, the distribution of TSS in the present study was the mean and SD of 13.2±8.6, and that score corresponded to the mild and moderate grades in the severity scale of Medsger et al![19] This low incidence may be partly related to racial differences. When the same severity score is applied to a Japanese population of SSc patients, there are less patients in the severe and end-stage groups![13] When the more severe types are defined as severe >30 and end-stage >40, and if these patients had been included in the present study, a higher incidence of ischemia and MIBG defect might have been found. In a study of 95 Japanese patients with SSc, 8-year follow-up revealed a diversity of myocardial involvement, such as diffuse or regional wall hypokinesis (n=7), cor pulmonale (n=10) and septal hypertrophy (n=12), and was related to type and specific antibodies![20] Although the frequency of severe involvement was not high, a long-term follow-up study of our study group would be informative.

Diastolic dysfunction was observed even without stress-induced ischemia and systolic dysfunction. ^{99m}Tc radiopharmaceuticals are suitable for gated studies, and a 16-frame per cardiac cycle was successfully performed for calculating the diastolic parameters![7,21–23] Simultaneous assessment of perfusion and ventricular function is considered convenient for clinical practice. Akincioglu et al studied the validity of diastolic dysfunction using QGS software, and concluded that gated SPECT could be used for the diastolic functional study![23] According to their results, TPF appeared to be a stable and more useful parameter, because of the dependency of PFR on sex, age and heart rate (HR). The present study also showed the usefulness of TPF rather than PFR for discriminating patients with diastolic dysfunction. Other diastolic parameters, such as one-third filling rate and filling fraction, might be used, but we selected PFR and TPF because they are widely used parameters in nuclear studies. Diastolic dysfunction indicated that myocardial stiffness or compliance was affected by the pathologic process in SSc. Diastolic dysfunction in the early stages has also been noted in a gated pool–pool study, and gated SPECT could have detected the same abnormality![24] Those researchers found that impaired diastolic relaxation of the

left ventricle was also detected in 10 of 24 patients with SSc.

Sympathetic abnormality was detected by MIBG, as shown by decreased uptake and rapid clearance. Some studies have indicated that autonomic dysfunction is extremely common in SSc. It is characterized by parasympathetic impairment and marked sympathetic overactivity, particularly in the early stage.[25] Moreover, significant abnormalities in cardiovascular reflexes have been found in patients with SSc, both in those with CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) and in those with diffuse involvement. Both sympathetic and parasympathetic dysfunction have been observed.[26] HR variability is reduced and sympathetic output increased in patients with SSc;[27] so a MIBG abnormality and rapid MIBG turnover may reflect sympathetic derangement in SSc. Gürtner et al reported that ^{123}I MIBG scintigraphy revealed an inhomogeneous reduction in 15 patients (83%).[8] The present study showed a lower incidence which may reflect differences in disease severity, technical differences, such as the ROI setting and collimator selection, and particularly the criteria for judging heterogeneity. However, if more severe types were included as discussed before, the incidence of MIBG defects may be more clearly identified.

MIBG and diastolic dysfunction seem to have independent diagnostic significance. Although the incidence of MIBG and diastolic abnormality was higher in the severe group, it was also observed in some of the less severe groups, resulting in fair correlation as a whole. In addition, the correlation between TPF/RR and MIBG WR was fair, and as was that between TSS and the MIBG or diastolic parameters. The reason for this is partly because TSS is a semiquantitative ordinal-scale value that reflects skin lesions. The cardiac involvement in SSc is multifactorial and may not show a simple linear correlation with skin scores. Moreover, if more end-stage patients had been included in the present study, a higher correlation between diastolic dysfunction and MIBG abnormality might have been found. Although an independent diagnostic significance of MIBG and diastolic dysfunctionswas suspected, the inter-factorial relationship is an important issue to be investigated. Thus, elucidating the mechanism of each abnormality and its prognostic significance requires further study, including long-term follow-up of patients.

Conclusion

In patients with SSc, a sympathetic abnormality is observed in both the mild and severe types in the MIBG study. Diastolic abnormality is observed by gated SPECT, even without ischemia, and correlates with the severity of SSc. Moreover, sympathetic and diastolic abnormalities were not directly correlated, suggesting independent pathologic significance. Thus, a scintigraphic approach can be a good adjunctive method for evaluating cardiac complications even in the early stage of SSc. Considering the possibility of early detection of cardiac dysfunction by nuclear studies, these patients should be followed up for future symptomatic cardiac complications.

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