Diastolic Dysfunction in Patients with Systemic Sclerosis Detected by Gated Myocardial Perfusion SPECT: An Early Sign of Cardiac Involvement

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Diagnosis of cardiac involvement is important for the management of patients with systemic sclerosis (SSc). This study was undertaken to determine the significance of gated myocardial perfusion SPECT in patients with SSc and whether diastolic function measured by gated SPECT is an early sign of cardiac complications. **Methods:** Thirty-four patients with SSc and 16 control patients were studied using exercise nongated and resting gated myocardial perfusion SPECT. The SSc was classified by the modified Rodnan total skin score (TSS) into high-TSS (score $\geq$ 10; n = 18) and low-TSS (score $<$ 10; n = 16) groups. Gated SPECT was performed using ^{99m}Tc-methoxyisobutylisonitrile with 16 frames per cardiac cycle and quantitatively analyzed by QGS software and Fourier filtering of the volume curve. The parameters of ejection fraction (EF), peak filling rate (PFR), one-third mean filling rate, and time to PFR (TPFR) were calculated. **Results:** A slight perfusion abnormality was observed in four and five patients in the low-TSS and high-TSS groups, respectively (not statistically significant). A decreased resting EF less than 55% was found in no and two patients in the low-TSS and high-TSS groups, respectively. TPFR was 166 $\pm$ 22, 168 $\pm$ 38, and 216 $\pm$ 82 ms (P = 0.05, high-TSS group versus low-TSS group; P = 0.04, control group versus high-TSS group) and TPFR/R-R interval was 0.18 $\pm$ 0.02, 0.19 $\pm$ 0.04, and 0.26 $\pm$ 0.09 (P = 0.01, high-TSS group versus low-TSS group; P = 0.005, control group versus high-TSS group) for the control, low-TSS, and high-TSS groups, respectively. **Conclusion:** Diastolic function can be evaluated by gated myocardial perfusion SPECT. Significant diastolic abnormalities were shown even in patients with normal perfusion and systolic function and were related to the severity of SSc.

Key Words: gated SPECT; diastolic function; systemic sclerosis; skin score; ^{99m}Tc-methoxyisobutylisonitrile

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Cardiac involvement in systemic sclerosis (SSc) includes arrhythmias, pericarditis, angina pectoris, congestive heart failure, and sudden death (*1–5*). Because renal involvement is no longer a major cause of death in SSc, cardiopulmonary involvement has been considered to be an important prognostic factor (*5,6*). Although the origin of the disease has not been fully understood, focal myocardial lesions ranging from contraction band necrosis to fibrosis (*1–3*) and reversible vasospastic abnormality in small coronary arteries (*7,8*) have been found to be an important mechanism in myocardial dysfunction.

Nuclear medicine studies with ^{201}Tl have shown that stress-induced ischemia and perfusion defects occur in the SSc group (*4,7–11*). A reduced coronary flow reserve has also been shown (*11*). However, our experience with SSc patients has been that perfusion defects and large areas of induced ischemia do not seem to be so common as described previously.

Recently, gated SPECT has become a common procedure in patients with ischemic heart disease (*12,13*). This quantitative technique has not, however, been used in patients with SSc. Moreover, although, in cases of ischemic heart disease, hypertension, and cardiomyopathy, myocardial involvement has been detected early by an evaluation of diastolic abnormalities (*14–18*), the feasibility of applying gated SPECT to assessment of diastolic function has not been investigated.

Thus, we hypothesized that gated perfusion SPECT can detect functional abnormalities earlier and more accurately than conventional nongated ^{201}Tl perfusion studies. Even if a perfusion defect is not observed, quantitative analysis of left ventricular contractility may detect functional abnormalities in an SSc population. Even if systolic dysfunction is not observed, some diastolic abnormalities may be present in the early stages of SSc. We investigated the

feasibility of evaluating the diastolic phase with gated SPECT.

MATERIALS AND METHODS

The study group consisted of 34 patients (3 men, 31 women; mean age ± SD, 56 ± 13 y) who were diagnosed with SSc in our dermatology department on the basis of the diagnostic criteria of the American Rheumatism Association (*19*). The final diagnosis, for hospitalized patients, was based on skin lesions and a general work-up of organ involvement including the lung, heart, kidney, and digestive system. The skin lesions were scored by the total skin score (TSS) as described below (*20–22*). The classification into diffuse and limited cutaneous SSc types was based on skin lesions, other clinical findings, and laboratory data, according to the method of LeRoy et al. (*20*). Patients with atrial fibrillation were excluded because the electrocardiogram (ECG) gating was expected to be inaccurate. Patients with other connective tissue disorders, such as polymyositis, dermatomyositis, systemic lupus erythematosus, and sarcoidosis, were also excluded, so that involvement by SSc alone could be evaluated. Exercise ECG, Holter ECG, and two-dimensional echocardiography were performed on all patients. The diffusing capacity of the lung was determined by carbon monoxide measurements. The glomerular filtration rate of the kidneys was measured using ^{99m}Tc DTPA and the method of Gates (*23*).

The control patients for gated SPECT consisted of 16 age-matched and sex-ratio–matched patients (2 men, 14 women; mean age, 50 ± 12 y). Treadmill-exercise ECG and gated ^{99m}Tc-methoxyisobutylisonitrile studies both at rest and during exercise were performed to rule out the possibility of angina pectoris (n = 12) and to monitor cardiac side effects before chemotherapy of lymphoma (n = 4). Echocardiography showed a normal chamber size, a normal wall thickness, and good ventricular contractility. The exercise study found no significant ECG changes indicating myocardial ischemia. The patients had no complications from diabetes mellitus or hypertension and were thus judged to have a low likelihood of cardiac disease.

TSS

Semiquantitative scoring of skin lesions was based on modified Rodnan criteria (*21,22*). The scleroderma was scored from 0 (normal) to 3 (severe) for 17 body surface areas. The summed skin score ranged from 0 to 51. In this study group, the mean TSS was 12 ± 9 and the range was 1–35.

Exercise and Resting Perfusion Imaging

The exercise study was performed using a supine bicycle ergometer, which started at 25 W and increased by 25 W. During symptom-limited peak exercise, 300–370 MBq ^{99m}Tc-methoxyisobutylisonitrile were intravenously injected and the exercise was continued for an additional 60–90 s. The second administration dose, for the resting study, was 600–740 MBq. The SPECT acquisition was started at least 40 min after each injection.

SPECT Data Acquisition and Reconstruction

A three-detector SPECT system (GCA 9300A/UI; Toshiba, Tokyo, Japan) was used for data acquisition and analysis. A total of 60 projection images were obtained, with 64 × 64 matrices over 360°. The acquisition time was 45 s for each projection. Hardware zooming was used for small patients (*24*). The first postexercise study was obtained without gating, and the second resting study was acquired with gating. A cardiac cycle was divided into 16 frames. The R-R interval and heart rate histogram were recorded to monitor arrhythmia. An average R-R interval of ±15% was accepted for gating.

The SPECT images were reconstructed by a standard filtered backprojection algorithm using a ramp filter. For preprocessing, a Butterworth filter with an eighth order and a cutoff frequency of 0.28 cycle/pixel (one pixel = 0.64 cm) was used. For reconstruction of nongated images, a Butterworth cutoff filter with a cutoff frequency of 0.30 cycle/pixel was used.

Analysis

Three nuclear medicine physicians visually judged exercise-induced ischemia and regional perfusion defects without knowing the severity of the skin lesions and reached a consensus. Both the gray-scale display on the film and a hard copy with rainbow color coding were used for interpretation.

Quantitative Gated SPECT (QGS) (version 2; Cedars-Sinai Medical Center, Los Angeles, CA), a commercially available software program, was used for calculating ventricular edges, volume, ejection fraction (EF), and functional maps. The algorithm for determining edges and calculating volume has been described and validated by Germano et al. (*12,13*).

Sixteen values for the ventricular volume were transferred to the microcomputer. Discrete Fourier transform was performed to calculate direct current components, fundamental frequency, and high-order harmonics. A fundamental wave and the second-to fourth-order harmonics were used to generate filtered volume curves. The filtered differentiation (dV/dt) curve was directly calculated by Fourier series. Examples of dV/dt parameters for two patients are shown in Figure 1. The peak filling rate (PFR) was defined as the maximum dV/dt value divided by end-diastolic volume (per second). The one-third mean filling rate was calculated as an average of dV/dt values in the first third of the filling time (per second). The time to PFR (TPFR) was measured from the time at end-systole to that at PFR (milliseconds). The ratio of TPFR (milliseconds) to R-R interval (milliseconds) was also calculated.

Statistical Analysis

Values were expressed as mean ± SD. Differences in variance and mean values were examined using a multiple comparisons test after a significant finding from one-way ANOVA. The Scheffé test was applied. Differences between the two groups were examined using the Student *t* test. Differences in the contingency table were examined using the χ^2 probability value. $P < 5\%$ was considered statistically significant.

RESULTS

Patient Classification

Patients were classified into a high-TSS group (score ≥ 10; mean, 19 ± 7) and a low-TSS group (score < 10; mean, 4 ± 3). Patient information is summarized in Table 1. No significant difference in age, age at onset, and disease duration was observed between the high-TSS group and the low-TSS group. In the low-TSS group, 3 diffuse and 13 limited cutaneous types of SSc were included, whereas in the high-TSS group, 15 diffuse and 3 limited cutaneous types were included ($P = 0.0002$ between the high-TSS group and the low-TSS group).

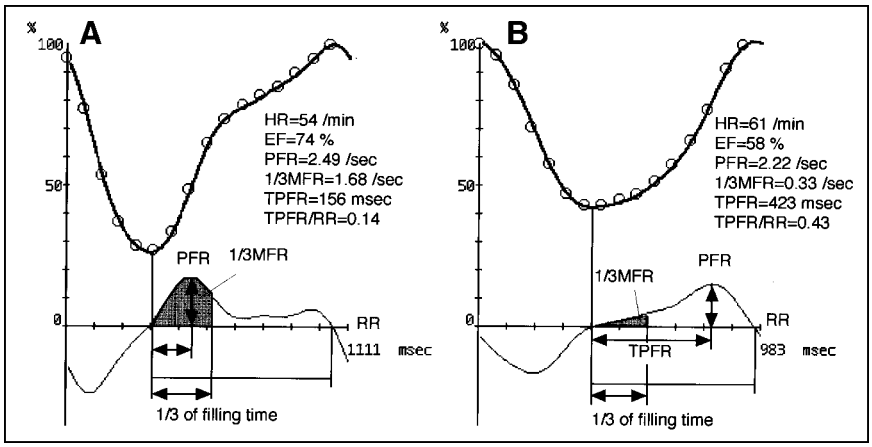

FIGURE 1. Examples of volume curves from two patients with SSc. Open circles are original data points. (A) Patient with limited cutaneous type and low TSS. All parameters of volume curve are within normal range. (B) Patient with diffuse cutaneous type and high TSS. Volume curve indicates low one-third mean filling rate (1/3MFR) and increased time to peak filling rate (TPFR). HR = heart rate; PFR = peak filling rate.

Perfusion Abnormality

Only a slight degree and a small region of inferoapical ischemia were suspected in two patients in the low-TSS group and one patient in the high-TSS group (not statistically significant [NS]). A slight degree of resting myocardial hypoperfusion was observed in two and three patients in the low- and high-TSS groups, respectively (NS). Either slight ischemia or hypoperfusion was seen in four and five patients in the low- and high-TSS groups, respectively (NS)

Parameters Based on Gated SPECT

Parameters calculated by QGS software and Fourier fitting are shown in Table 2. Heart rate and end-diastolic volume did not differ significantly among the groups. Although average EF did not differ significantly among the groups, two patients in the high-TSS group had an EF less than 55%. These two patients had high skin scores (30 and 24). The fractional shortening measured on echocardiography was 37% ± 5% and 41% ± 6% in the low- and high-TSS groups (P = NS), respectively. The PFR did not differ significantly among the groups. The one-third mean filling rate was slightly low in the high-TSS group (P = 0.017). The TPFR and TPFR/R-R interval were increased in the high-TSS group (P = 0.015 and 0.002, respectively). If an abnormal TPFR/R-R interval is defined as ≥ 0.22 (average + 2 SD of the control group), abnormal filling was observed in one (6%), three (18%), and nine (50%) patients in the control, low-TSS, and high-TSS groups (P = 0.01), respectively.

TABLE 1
Classification by TSS

Parameter	Low TSS	High TSS	*P*
n	16	18	
Age (y)	56 ± 10	55 ± 15	NS
Age of onset (y)	44 ± 15	46 ± 17	NS
Disease duration (y)	13 ± 12	7 ± 13	NS
Male:female	2:14	1:17	NS
Type			0.0002
Limited	13	3	
Diffuse	3	15	
TSS	<10	≥10	
	4.0 ± 2.5	19.2 ± 6.7	<0.0001*

*Definition of classification.
NS = not statistically significant.

Other Abnormalities

In the high-TSS group, Holter ECG showed frequent multiform premature ventricular contractions (PVC) in four patients, a second-degree atrioventricular block (Wenckebach block) in one patient, and an incomplete right bundle branch block in one patient. Frequent PVC or supraventricular premature contractions (SVPC) was seen in two patients with a low TSS and in six patients with a high TSS (NS). Sporadic innocent PVC and SVPC were observed in 10 and 12 patients in the low- and high-TSS groups, respectively (NS). The ST-T abnormality was observed in only one patient in the high-TSS group. The glomerular filtration rate of both kidneys was 87 ± 23 mL/min and 72 ± 21 mL/min for the low- and high-TSS groups (P = 0.057 [NS]), respectively, although the latter group showed a relatively low glomerular filtration rate. The diffusing capacity measured by carbon monoxide diffusion in the lung was significantly low in the high-TSS group (52% ± 21%, P = 0.017) compared with that in the low-TSS group (69% ± 15%).

DISCUSSION

Autopsy findings of myocardial fibrosis in SSc have been reported to be common (*1–3*). Clinical diagnosis of myocardial involvement, however, is less frequent. When cumulative survival rate was analyzed (*5*), heart involvement was one of the most important prognostic factors. If the heart was involved, lung involvement made little difference

TABLE 2
Comparison of Gated SPECT Parameters

Parameter	Control	Low TSS	High TSS	ANOVA *P*	*P* between each group
n	16	16	18		
Heart rate (per minute)	65 ± 7	68 ± 11	71 ± 8	NS	
End-diastolic volume (mL)	73 ± 19	55 ± 10	58 ± 18	NS	
Ejection fraction (%)	68 ± 9	73 ± 9	71 ± 12	NS	
Ejection fraction < 55%	0 (0%)	0 (0%)	2 (11%)	NS	
Diastolic parameters					
Peak filling rate (PFR) (per second)	2.46 ± 0.45	2.76 ± 0.44	2.74 ± 0.53	NS	
One-third mean filling rate (per second)	1.52 ± 0.25	1.57 ± 0.31	1.25 ± 0.42	0.017	L, H(0.03); C, H(0.08)
Time to PFR (ms)	166 ± 22	168 ± 38	216 ± 82	0.015	L, H(0.05); C, H(0.04)
Time to PFR/R-R interval	0.18 ± 0.02	0.19 ± 0.04	0.26 ± 0.09	0.002	L, H(0.01); C, H(0.005)

NS = not statistically significant; L = low TSS; H = high TSS; C = control.

in survival rate. The simplest way to assess cardiac involvement clinically is through ECG, which evaluates arrhythmias and conduction abnormalities. In addition, pericarditis, congestive heart failure, or low voltage was observed. Considering the poor prognosis in patients with cardiac involvement, quantitative methods are desirable for early diagnosis, treatment monitoring, and prognostic evaluation.

For classification, we used the modified Rodnan method, which has been in recent international use to quantify the severity of SSc. The score is based on cutaneous thickness assessed for 17 body surface areas using a 0–3 scale. Good reproducibility has been reported for the scoring technique, and the score has correlated with the severity of disease activity (*21*,*22*,*25*). Diffuse scleroderma associated with a high TSS has indicated a poor prognosis and a high incidence of involvement in other organs, such as the kidney, heart, and lungs. This classification has generally matched well with the limited and diffuse cutaneous types reported by LeRoy (*20*).

Myocardial perfusion studies, mainly using ^{201}Tl, have been performed to investigate stress-induced ischemia and myocardial damage. Using exercise ^{201}Tl and radionuclide ventriculography, Follansbee et al. (*4*) studied 26 patients with SSc and found that 20 patients showed abnormal findings on thallium scans, including 10 with reversible ischemia and 18 with fixed defects. The mean resting EF was also lower in patients with a perfusion defect. In patients with larger thallium perfusion defects, a significantly increased risk of subsequent cardiac events or death has also been reported (*10*). Reversible cold-induced ischemia was found in 10 of 13 patients by a ^{201}Tl study (*7*). In addition, reduced coronary flow and reduced perfusion reserve were reported in seven patients with SSc (*11*). These findings have indicated that abnormalities of microcirculation (intermittent vascular spasm or intramyocardial Raynaud's phenomenon) and focal scattered fibrosis may result in stress-induced ischemia and manifest as focal defects on a myocardial perfusion scan.

Compared with these studies, no significant segmental defect or induced ischemia was observed in this study. Conversely, we found only a minor degree of perfusion abnormality. Because scoring by Rodnan TSS was common even in different hospitals, the low degree of damage we found is partly explained by differences in disease severity. Scores of 0–9, 10–35, and more than 35 usually correspond to SSc that is mild, moderate, and severe, respectively (*25*). Thus, our study group might not include the most severe type of SSc. Another explanation may be differences in the sex and race of the patients. The previous reports found that men had a poorer prognosis than women, and racial differences were also noted (*5*). Special aspects of the Japanese population and the prevalence in women in our study may be the cause of the relatively low degree of myocardial damage that we found (*26*,*27*). The use of ^{111}In-antimyosin and ^{123}I-metaiodobenzylguanidine has been described (*28*,*29*), but further investigation is necessary to validate these radiopharmaceuticals.

Abnormalities in diastolic function were found in half the high-TSS group, although a decrease in EF was observed in only two patients. Pace et al. (*30*) reported impaired relaxation and diastolic asynchrony in SSc using radionuclide angiography. However, whether a relationship existed with the severity of SSc was not evaluated. Because myocardial fibrosis increases with the progress of SSc, a decrease in left ventricular contractility may be anticipated. Even patients with a normal resting EF may have a reduced functional reserve for exercise, but we did not evaluate EF during exercise. However, in ischemic heart disease, hypertrophic cardiomyopathy, and hypertensive heart diseases, diastolic dysfunction may occur even without any systolic dysfunction (*14–18*). Various factors such as myocardial stiffness, wall elasticity, compliance, incomplete relaxation, and ventricular pressure may be involved in diastolic dysfunction (*31–33*), and a similar mechanism may also be at work in SSc. From our results, we speculate that diastolic abnormal-

ity is an early characteristic of myocardial involvement in SSc.

The reliability of diastolic function has been established in gated blood-pool studies (*14–18,30*) but not in gated myocardial SPECT. In our preliminary study, diastolic dV/dt parameters derived from gated SPECT with 12 frames per cardiac cycle were compared with those from a gated blood pool study with 24 frames per cardiac cycle in 20 patients (*34*). The correlation coefficients were 0.73 for PFR, 0.85 for one-third mean filling rate, and 0.90 for EF. Inaccuracy of diastolic parameters, however, has been noted in some patients. Therefore, we used 16 frames per cardiac cycle, which is a reasonable compromise in current gated SPECT studies. To obtain a sufficient myocardial count by 16-frame division, we used a triple-detector system. A dual-detector system with a rectangular configuration is also an option for this purpose. To evaluate the diastolic function more precisely, we used Fourier fitting rather than numeric calculation of derivatives. The last part of the volume curve may have been underestimated by fluctuation of the R-R interval during acquisition. However, because edge detection was based on gaussian fitting by the QGS software, a slight count underestimation in the last part would not influence the volume determined automatically. In fact, we did not see a sudden drop of curve in the last frames in this series. Moreover, this study clearly indicated that evaluation of diastolic function was valid even by gated SPECT studies. Thus, calculation of diastolic dV/dt routinely, even for other types of cardiac diseases, may be helpful using a gated SPECT study if more than a 16-frame division is used. Patients with atrial fibrillation were not included in this study because of inaccuracy in evaluating the diastolic phase. Frequent PVC or SVPC during acquisition will be inappropriate in gated SPECT. In this series, all patients showed only a few rejected beats during acquisition. Consequently, the result was considered reliable.

Who are candidates for a gated myocardial study? Patients with a TSS of 10 or higher should be studied by gated SPECT, and diastolic function should be carefully evaluated. Patients with a diffuse cutaneous type of SSc are also good candidates for gated SPECT. Although many patients may show no clinical symptoms during a routine work-up for SSc, diastolic dysfunction can be an early sign of cardiac dysfunction, and patients showing such dysfunction should be followed up. Moreover, patients in whom Holter ECG reveals arrhythmia and patients with clinical signs of ischemia, effusion, and heart failure should be examined with a stress perfusion study. Although patients with these severe manifestations were not included in our population, a study that includes such patients would help in their management. Further follow-up studies are required to elucidate whether diastolic abnormalities are reversible with treatment and whether they correlate with the progress of systolic and perfusion abnormalities. Lastly, the prognostic significance of each parameter should be determined. Compared with gated blood-pool studies, which can be performed both at rest and during exercise, gated SPECT can be performed only at rest. However, the merit of gated perfusion SPECT is its ability to simultaneously assess exercise–rest perfusion and resting ventricular function. Because myocardial perfusion SPECT, particularly gated, seems to be underutilized in this field, such uses should be further investigated.

CONCLUSION

In addition to calculating EF and ventricular volume, gated SPECT can evaluate diastolic function. Diastolic abnormalities, although also observed in patients with normal perfusion and systolic function, may be an early sign of cardiac dysfunction in patients with mild to moderate SSc.

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