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# Dipyridamole stress thallium perfusion scan for evaluating myocardial involvement in systemic sclerosis

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**Abstract** To evaluate the usefulness of a dipyridamole stress thallium-201 (Tl-201) perfusion scan in detecting myocardial involvement in systemic sclerosis we performed Tl-201 scans, electrocardiograms (ECG), and echocardiograms (UCG) on 24 patients with systemic sclerosis (11 diffuse type, 13 limited type) sequentially selected randomly over an 8-month period, and compared the findings. Cardiac catheterization, coronary angiography (CAG), and right ventricular endomyocardial biopsy were performed as necessary. Of the 24 patients, Tl-201 scans revealed fixed defects (FDs; myocardial fibrosis) and/or reversible defects (RDs; myocardial ischemia) in nine patients, whereas ECG and UCG revealed defects in four and three patients, respectively. Biopsy specimens obtained from the three patients with FDs also showed both ECG and UCG abnormalities indicative of myocardial fibrosis despite their normal appearance with CAG. Autopsy findings on the heart of a patient who died of acute heart failure showed myocardial fibrosis predominantly in the left anteroposterior wall. This was consistent with the FDs area detected using the Tl-201 perfusion scan. In a patient with chronic heart failure, left ventriculography showed a decrease in the anterior wall motion of the left ventricle which coincided with the FDs area in the Tl-201 perfusion scan. In conclusion, dipyridamole stress Tl-201 scanning is useful for evaluating myocardial involvement in systemic sclerosis.

**Key words** Dipyridamole stress thallium-201 perfusion scan · Myocardial involvement · Systemic sclerosis

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## Introduction

Systemic sclerosis (SSc) is a multiorgan disorder characterized by microvascular abnormality, inflammation, and fibrosis. SSc lesions involve not only the skin but also a variety of internal organs. Heart, kidney, and lung are the three major organs which are affected, and that influences the survival rate. However, neither the etiology nor pathogenesis of SSc is clear.[1]

Cardiac involvement in SSc (scleroderma heart disease) was first reported by Weiss et al.[2] Scleroderma heart disease involves the pericardium and myocardium. The main feature of myocardial involvement is myocardial fibrosis.[3–5] A histopathological characteristic of myocardial fibrosis is a diffuse and patchy process which is distinguishable from myocardial fibrosis due to coronary atherosclerosis in that it is equally distributed throughout the right and left ventricles.[2,6–8] There is a notable discrepancy between the prevalence of clinical myocardial involvement[6,9,10] and the prevalence of myocardial fibrosis found at autopsy.[7,8] While clinically evident myocardial involvement is uncommon, myocardial fibrosis is present in the majority of patients at autopsy.[8]

To detect myocardial involvement, electrocardiograms (ECG), echocardiograms (UCG), radionuclide ventriculograms, and myocardial scintigrams have been used.[11] ECG is a useful method for evaluating the patient's probability of survival.[12,13] Abnormalities detected by ECG are diverse, including atrial and ventricular arrhythmias, myocardial infarction patterns, left and right ventricular hypertrophy, and abnormalities in the conduction system, including right bundle branch block, left bundle branch block, left anterior fascicular block, and high-grade heart block. Of these, a "septal infarction pattern," defined as abnormal Q waves in $V_1$ and $V_2$ in the absence of QRS complexes prolongation (QRS duration greater than 120 msec), and "ventricular

conduction abnormalities" are reported as ECG abnormalities associated with myocardial fibrosis.[14]

Stress thallium-201 (Tl-201) scintigraphy is an accurate method of detecting ischemic heart diseases.[15] In SSc, this method has been reported to detect myocardial involvement using maximal exercise by treadmill[16] or cold exposure[17] as the stress. These studies claimed that Tl-201 scintigraphy was an especially useful examination tool since in many cases it revealed abnormalities in patients who otherwise showed no clinical evidence of cardiac involvement. However, patients with SSc complicated with pulmonary fibrosis, pulmonary hypertension, severe Raynaud's phenomenon, and/or skin ulcers may not be able to perform maximal exercise or to bear cold exposure. In the field of cardiology, dipyridamole perfusion has recently been used successfully in Tl-201 scintigraphy,[18] replacing maximal exercise on a treadmill. The application of dipyridamole to Tl-201 scintigraphy may be especially beneficial in dealing with SSc patients since it eliminates the discomfort accompanying maximal exercise or cold exposure. The present study examined the usefulness and appropriateness of dipyridamole perfusion Tl-201 scanning to detect abnormalities in SSc patients.

## Materials and methods

### Patients

The study population consisted of 24 SSc patients (7 male, 17 female). The patients were sequentially selected randomly over a 8-month period (May–December 1993); informed consent was obtained from each. Diagnoses of SSc were based on the American Rheumatism Association's preliminary criteria for systemic sclerosis.[19] Of the 24 patients, 11 were classified as "diffuse type" and 13 as "limited type," following the system proposed by LeRoy et al.[20] Patients included in the study did not have pulmonary hypertension, renal crisis, or thyroid disease complications. At the time of the study, 11 patients were being treated with D-penicillamine, 4 with bucillamine, 9 with prednisolone (PSL, <10 mg/day), 10 with prostaglandin, 9 with vitamin E, 3 with platelet antiaggregates, and 2 with Ca channel blockers.

Muscle involvement was judged by the demonstration of myositis by biopsy or by the presence of at least two of the following factors: myalgia, muscle weakness, and elevated serum level of creatine kinase (CK), aldolase, or both.

### Dipyridamole Tl-201 perfusion scans

Dipyridamole was administered intravenously to the patient for 4 min at a rate of 0.142 mg/kg/min (total 0.568 mg/kg).[18] Immediately after the dipyridamole infusion, the patient walked on the spot for 3 min. Pulse rate, blood pressure, and ECG were monitored during this procedure. Seven minutes after the start of the dipyridamole infusion, intravenous administration of 120 Mbq Tl-201 chloride was initiated. Tomographic imaging was started within 8 min of the Tl-201 injection (stress imaging), and 3 h later the resting patient received an additional dose of 30 Mbq Tl-201 chloride (delayed imaging). Tomographic imaging was started again 30 min after the reinjection. The images were reconstructed into transverse sections and then reformatted to provide horizontal and vertical long- and short-axis sections. The sections were reviewed visually and also compared using a computer database.

### Assessment of cardiac involvement

Cardiac involvement was examined by dipyridamole Tl-201 perfusion scanning, ECG, and UCG. For each patient, the three examinations were performed within 1 month of each other. Cardiac catheterization, coronary angiography (CAG), and right ventricular endomyocardial biopsy were performed by conventional methods[21] as necessary. The findings were evaluated by two cardiologists working independently, neither of whom found clinical problems or any other abnormalities on ECG and UCG.

### Statistical analysis

Fisher's exact probability test was used to determine the frequencies of clinical features, and Student's *t*-test was used to compare the means of continuous variables. Significance was established at $P < 0.05$.

## Results

### Dipyridamole Tl-201 perfusion scan compared with ECG or UCG

Dipyridamole Tl-201 perfusion scanning revealed abnormalities in 9 of 24 patients (38%). In this examination, two types of perfusion defects were observed. First, perfusion defects were detected at stress imaging, but these was a redistribution of Tl at delayed imaging, indicating the presence of reversible defects (RDs) which may be caused by myocardial ischemia. Second, perfusion defects were detected at both stress imaging and delayed imaging, indicating the presence of fixed defects (FDs) which may have been caused by myocardial fibrosis. Three patients showed both RDs and FDs, and six showed only RDs.

The findings of dipyridamole Tl-201 perfusion scans were compared with those of ECG and UCG (Table 1). The incidence of abnormalities shown by dipyridamole Tl-201 perfusion scans was higher than those shown by ECG (four patients; 17%) or UCG (three patients; 13%). Abnormal ECG findings included case IS with a complete atrioventricula (AV) block as a ventricular conduction abnormality (VCA) and VT, case YI with left axis deviation (LAD) as a VCA, premature ventricular contraction (PVC), and bilateral atrial overload, case HW with a septal infarction pattern and VT, and case YO with a right bundle

**Table 1.** Dipyridamole Tl-201 perfusion scan (D-TS) compared with ECG and UCG

| Case | D-TS | | ECG | UCG |
|---|---|---|---|---|
| | RD | FD | | |
| IS[a,b] | + | + | VCA (complete AVB), VT, PVC | LVH |
| YI[b] | + | + | VCA (LAD), PVC, LA, RA overload | Reduced LV, wall motion |
| HW[b] | + | + | Septal infarction pattern, ST-segment depression, VT, PAT | LA enlargement |
| YO[c] | + | − | VCA (RBBB), LAD, LA overload, Poor R progression | WNL |
| MI[c] | + | − | WNL | WNL |
| TN[c] | + | − | WNL | WNL |
| MC[c] | + | − | WNL | WNL |
| KM | + | − | WNL | WNL |
| HM | + | − | WNL | WNL |

[a] Autopsy
[b] Myocardial biopsy
[c] D-TS repeated
RD, reversible defect; FD, fixed defect
ECG findings: VCA, ventricular conduction abnormality; AVB, atrioventricular block; VT, ventricular tachycardia; PVC, premature ventricular contraction; LAD, left axis deviation; LA, left atrium; RA, right atrium; PAT, paroxysmal atrial tachycardia; RBBB, right bundle branch block; WNL; within normal limit
UCG findings: LVH, left ventricular hypertrophy; LV, left ventricule

branch block as a VCA. Abnormal UCG findings were left ventricular hypertrophy (LVH) in case IS, reduced left ventricular wall motion in Case YI, and left atrial enlargement in Case HW. No patient had an abnormal ECG or UCG with a normal dipyridamole perfusion scan. Three cases (IS, YI, HW) with FDs also showed both ECG and UCG abnormalities. Biopsy specimens obtained from these three cases indicated myocardial fibrosis despite a normal appearance during CAG.

To date, four patients (superscript "c" in Table 1) have had follow-up dipyridamole Tl-201 perfusion scans 6–12 months after the initial scan. In three of the four patients, RDs were present in similar areas to those of the second scan. Another patient (case MC) was judged to be borderline at the first scan and appeared normal in a scan performed 1 year later (data not shown).

## Clinical features in SSc with myocardial involvement

To analyze the clinical characteristics of SSc patients with myocardial involvement, the backgrounds of the patients who were judged to be positive in the dipyridamole thallium-201 perfusion scan were compared with those who were judged to be negative. The number of positive males was significantly higher than the number of negative males ($P < 0.02$), but otherwise there were no marked differences between the two groups. The frequency of diffuse sclerosis was not significantly different. Likewise, other clinical features such as esophageal dysmobility, tuft absorption, elevated erythrocyte sedimentation rate (ESR), hypercholesterolemia, hypergammaglobulinemia, or antibody to SSA/Ro were not dissimilar in the two groups (data not shown).

## Representative cases

Case IS was a 68-year-old man with diffuse scleroderma. His family doctor found a complete heart block in 1990, at which time a cardiologist recommended implantation of a permanent pacemaker; IS rejected the recommendation. The patient was admitted to our institute on March 25, 1993, complaining of dyspnea on exertion. The onset of scleroderma was not noticed because he had not experienced Raynaud's phenomenon, arthritis, or swollen hands. Upon admission, skin sclerosis was present on both hands and the skin on his face, trunk, and upper and lower extremities was atrophic. His fingers were shortened, and tuft absorption was detected by X-ray examination of his fingers. He had a 1280-fold nucleolar pattern of antinuclear antibody, as determined by the indirect immunofluorescence method. An ECG showed complete atrioventricular block (AVB). Ventricular tachycardia and premature ventricular contractions were noted in a 24-h continuous ECG (Holter monitor).

A dipyridamole Tl-201 perfusion scan was performed on March 30, 1993. FDs were present at the left anteroinferior wall at stress imaging, and a redistribution of Tl (RDs) was observed in part of the anterior wall (Fig. 1). A CAG examination performed nearly 2 weeks later (April 12, 1993) failed to show any abnormalities, suggesting that the vessels involved were smaller than could be detected by CAG.

The patient died of low-output heart failure 4 months after the Tl-201 perfusion scan. The heart wall was thickened, and gray-white portions suggested the presence of fibrosis. These findings were observed predominantly in the left anteroposterior wall, and were consistent with the FDs area detected by the Tl-201 perfusion scan, but in almost all the walls (Fig. 2A). Masson staining of the myocardium revealed massive myocardial deletion and fibrosis around the small vessels and among the muscle fibers (Fig. 2B,C), and massive fibrosis in the inside and outside portions of atrioventricular nodules (Fig. 2D). These pathological lesions might have been responsible for the complete AV block diagnosed in 1990, in addition to the other arrhythmias observed in 1993.

Case YI was a 54-year-old man with limited scleroderma. He was transferred to our institute because of hypoxia due to chronic heart failure. A dipyridamole Tl-201 perfusion scan showed a large FD and a large RD at the left anterior wall (Fig. 3) despite a normal appearance during CAG. A left ventriculogram (LVG) showed a decrease in the anterior wall motion of the left ventricle, which was in accord with the FD area in the dipyridamole Tl-201 perfusion scan. The calculated ejection fraction rate was only 27%. An endomyocardial biopsy obtained from the right ventricule showed myocardial fibrosis.

Case YO was a 26-year-old man with limited scleroderma. He had experienced Raynaud's phenomenon since

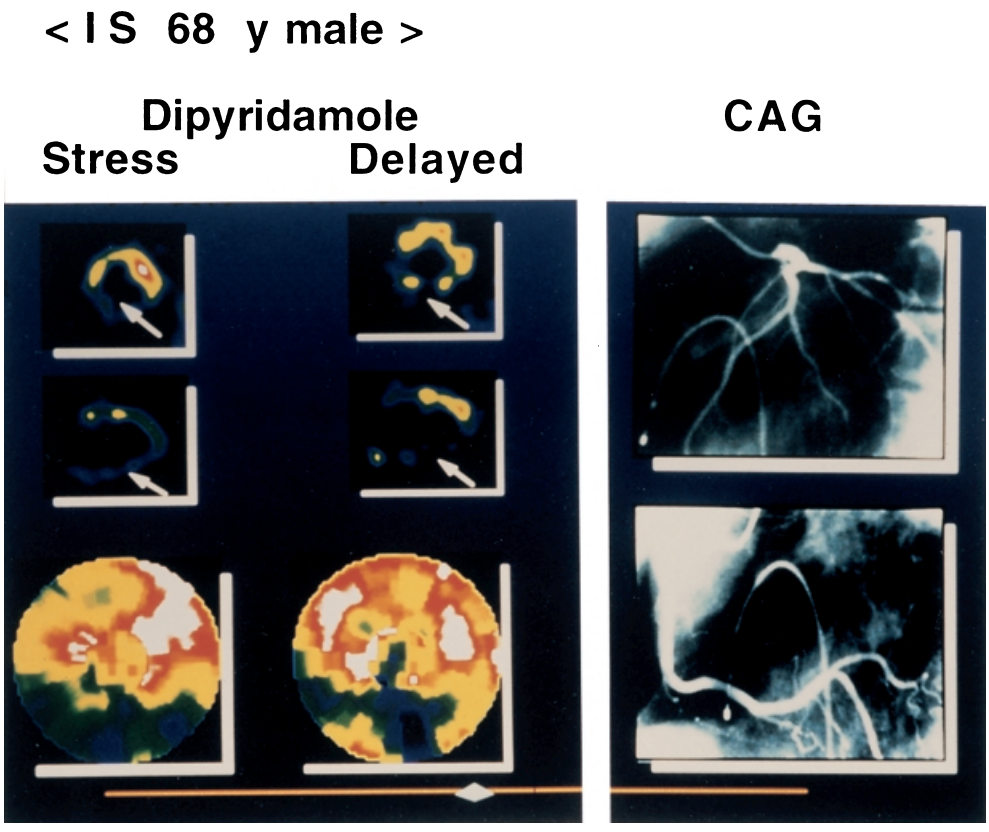


**Fig. 1.** Dipyridamole thallium perfusion scans and coronary angiograms in case IS, a 68-year-old man with diffuse scleroderma. The *left panel* shows dipyridamole stress thallium perfusion scans (*left*, stress imaging; *right*, delayed imaging; *top*, short axis section; *middle*, vertical long axis section; *bottom*, bull's eye). Perfusion defects are present in the left anteroinferior wall in stress imaging; these defects were also detected by delayed imaging, indicating fixed defects (*arrows*). Thallium redistributions are observed in part of the anterior wall, indicating reversible defects. The *right panel* shows the findings of a coronary angiography (*CAG*). Neither stenosis nor obstructions were detected in the left (*top panel*) and right (*bottom panel*) coronary arteries

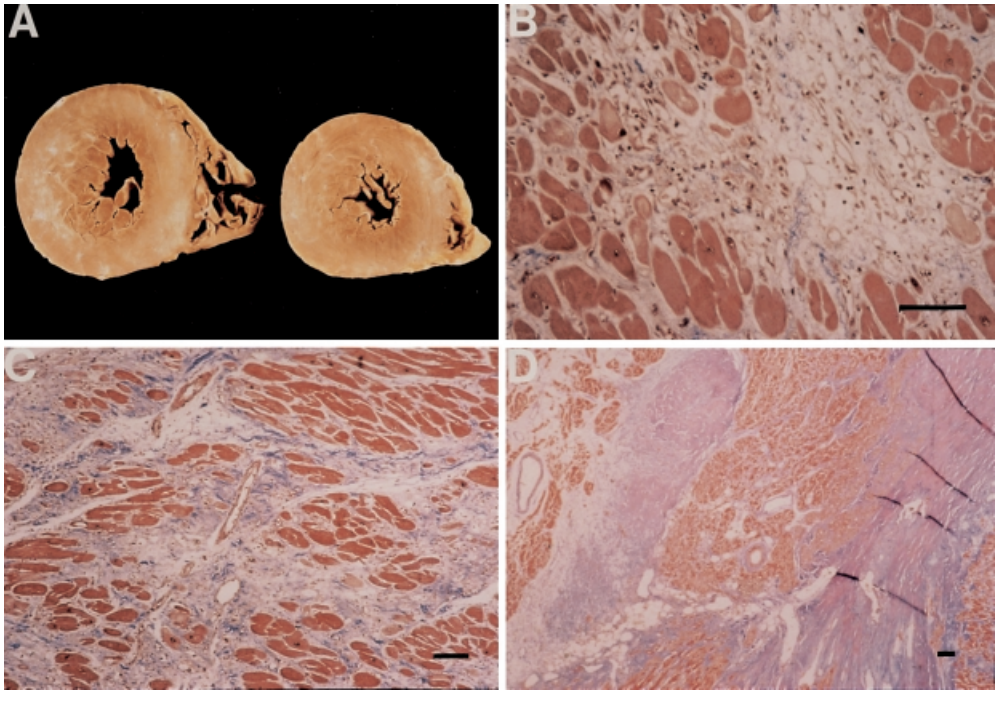


**Fig. 2.** Autopsy findings in case IS, who died of acute heart failure 4 months after the dipyridamole thallium-201 perfusion scan. **A** Transverse heart section; the heart wall is thickened and gray–white portions, suggesting the presence of fibrosis, are observed predominantly in the left anteroposterior wall. This is consistent with the lesions detected by the Tl-201 perfusion scan, but there it was in almost all walls. **B**, **C** Masson staining of myocardium; massive myocardial deletion and fibrosis are observed around small vessels and among muscle fibers. **D** Masson staining of atrioventricular nodules; massive fibrosis is also observed inside and outside the atrioventricular nodules. These pathological lesions might be responsible for the complete atrioventricular block in addition to the other arrhythmias. *Bars* 40 μm

1983, and had been diagnosed with subclinical Sjögren syndrome with myositis (maximum serum CK, 755 mU/ml). His ECG showed only a first-degree AV block. The myositis improved immediately with prednisolone (PSL) treatment (40 mg/day) and no reactivation of the symptoms was observed without additional PSL administration. He was transferred to our institute because of swellings on his hands and fingers that had been evident since 1990. His

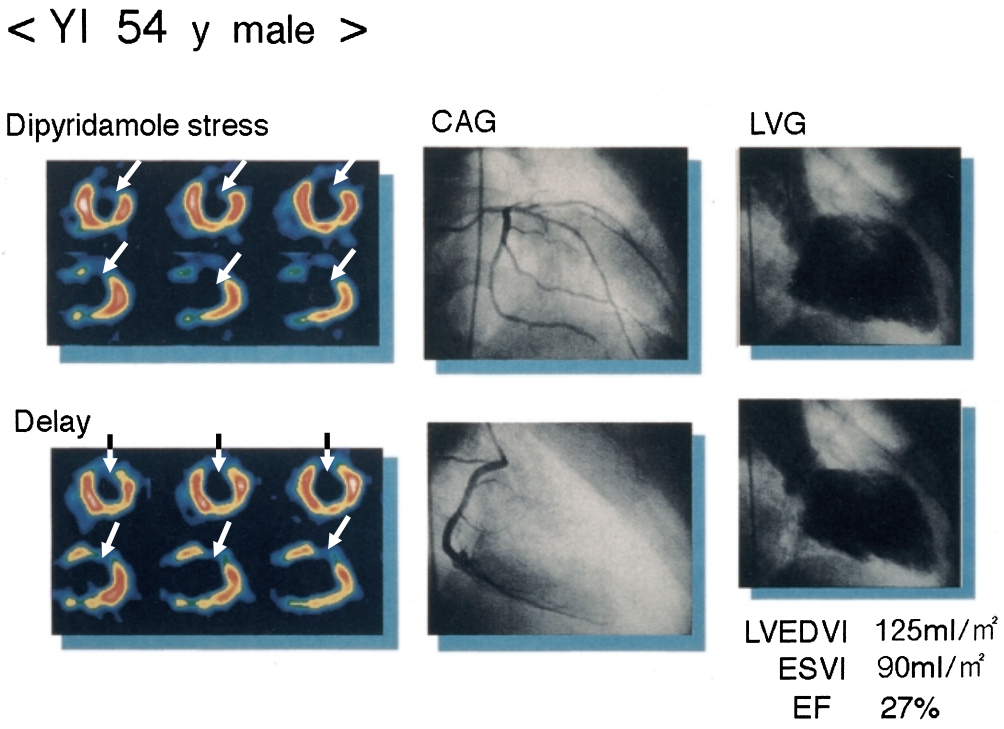


**Fig. 3.** Dipyridamole thallium perfusion scan, coronary angiogram, and left ventriculography findings in case YI, a 54-year-old man with limited scleroderma. *Left-hand panel*, dipyridamole thallium perfusion scans showing stress (*upper*) and delayed (*lower*) imaging. The upper parts of both the stress and delayed imagings show short axis sections, and the lower parts show vertical long axis sections. A large fixed defect and a reversible defect are present in the left anterior wall. *Middle panel*, coronary angiogram showing normality in both the left (*upper panel*) and right (*lower panel*) coronary arteries. *Right-hand panel*, left ventriculogram (LVG). A decrease in the anterior wall motion of the left ventricle is shown by the comparison between diastole (*upper panel*) and systole (*lower panel*); the calculated ejection fraction rate is 27%. *LVEDVI*, left ventricular end-diastolic volume index; *ESVI*, end-systolic volume index; *EF*, ejection fraction

ECG upon admission in September 1993 revealed not only a first-degree AV block, but also an incomplete right bundle block, left axis deviation, and poor R progression. However, no UCG abnormalities were observed. The first dipyridamole Tl-201 perfusion scan performed on October 15, 1993, showed patchy RDs in the anterior and inferior walls. After being discharged from the hospital on October 19, he frequently felt chest discomfort when he touched cold wet blooms or was thinly dressed in winter. The repeated perfusion scan on May 21, 1994, revealed clear RD areas in the anterior and inferior walls, but no FDs in the delayed scan (data not shown).

## Discussion

The stress Tl-201 perfusion scan is a particularly useful examination tool to detect myocardial involvement in SSc, since in many cases it reveals abnormalities in patients who otherwise show no clinical evidence of cardiac involvement.[16,17] However, the use of either maximal exercise on a treadmill or cold exposure to induce stress may not be appropriate for SSc patients, especially those whose illness is complicated with pulmonary fibrosis, pulmonary hypertension, severe Raynaud's phenomenon, and/or skin ulcers. The application of dipyridamole to Tl-201 scintigraphy may be especially beneficial in dealing with SSc patients, since it eliminates the discomfort accompanying maximal exercise or cold exposure. Stress induced by dipyridamole, a coronary dilator that can be used safely, is less invasive, and therefore might be more suitable for SSc patients with complications. The mechanism of myocardial ischemia induced by dipyridamole as the stress or is considered to be a "blood stolen" phenomenon caused by the difference in coronary dilation between normal and affected arteries. A possible angina attack caused by the blood stolen phenomenon is apparently a minor problem; neither angina attacks or ECG changes were observed during the course of this study.

To evaluate the usefulness of the dipyridamole stress Tl-201 perfusion scan in detecting myocardial involvement, we compared the findings of Tl-201 scans with those of ECG and UCG (see Table 1). To avoid biased judgments, the patients were sequentially selected randomly over an 8-month period, and their clinical records were not provided to the two cardiologists who worked independently, performed the perfusion scans, and judged the results. Of the 24 patients, dipyridamole stress Tl-201 scans revealed FDs and/or RDs in nine patients (38%). Biopsy specimens obtained from the three patients (IS, YI, HW) with FDs also showed abnormalities indicating myocardial fibrosis on both ECG and UCG, despite having a normal appearance on CAG. Of the patients with ECG abnormalities, two cases had VCA and one had a septal infarction pattern. No

patient had an abnormal ECG or UCG with a normal dipyridamole perfusion scan. At the autopsy, the presence of fibrosis in the heart of case IS, observed predominantly in the left anteroposterior wall (see Fig. 2A), was consistent with the FDs area detected by the dipyridamole Tl-201 perfusion scan (see Fig. 1). Moreover, in case YI, who had chronic heart failure, LVG showed a decrease in the anterior wall motion of the left ventricle, which was in accord with the FD area in the dipyridamole Tl-201 perfusion scan. These findings supported the concept that the dipyridamole Tl-201 perfusion scan is useful for detecting myocardial involvement in SSc.

The dipyridamole Tl-201 perfusion scan was more sensitive (38%) than ECG (17%) or UCG (13%) for detecting patients with myocardial involvement. Similar findings were reported by Anvari et al.[22] They assessed the incidence and extent of cardiac involvement in SSc patients with no apparent cardiac symptoms. Their findings showed that the frequency of abnormalities by dipyridamole stress-reversible Tl-201 myocardial perfusion (6 of 14 patients, 43%) was higher than the ECG abnormalities (5 of 18 patients, 28%) we considered to be VCA, or the UCG abnormalities (1 of 18 patients, 6%) described as LVH. No studies of dipyridamole Tl-201 perfusion scans on healthy volunteers as normal controls have been reported. Candell-Riera et al.[23] reported that the abnormalities shown by cold-stress Tl-201 scintigraphy were higher (64%) than abnormalities shown by ECG (6%), including right bundle branch block, and premature atrial beats in 63 patients with limited SSc. No LVH or reduced LV wall motion was detected by UCG, but systolic pulmonary arterial hypertension was found in 14% of cases.

The same study[23] also showed the frequencies of the abnormalities found by cold-stress Tl-201 scintigraphy in 57% of 47 patients with Raynaud's phenomenon, as defined by LeRoy and Medsger,[24] and in 5% of 20 healthy volunteer controls. Alexander et al.[17] reported that all of 13 patients with SSc, as compared with none of nine normal controls, showed abnormalities by cold-stress Tl-201 scintigraphy.

The high frequency of abnormalities found using a stress Tl-201 perfusion scan may be related to the hypothesis[8] that myocardial involvement in SSc is secondary to ischemic injury resulting from an abnormality in the intramyocardial circulation (an intramyocardial Raynaud's phenomenon), an injury that eventually results in fibrosis. The finding that these is a high prevalence of myocardial contraction band necrosis, a histological lesion seen in the setting of reperfusion injury, and that the presence of this lesion appears to correlate with the extent of fibrosis support this hypothesis. The histopathological characteristics of myocardial fibrosis is a diffuse and patchy process which is distinguishable from myocardial fibrosis due to coronary atherosclerosis.[2,6–8] Compared with a stress Tl-201 perfusion scan to induce ischemia, ECG and UCG, which do not require stress, may not be appropriate to detect this type of lesion.

The widely used dipyridamole Tl-201 perfusion scan (38%) might be somewhat less sensitive than a Tl-201 perfusion scan performed during exercise stress. Using the latter procedure, Follansbee et al.[25] reported that 14 of 22 patients (64%) with CREST syndrome and 20 of 26 patients (77%) with diffuse scleroderma exhibited abnormalities. The differences in frequency between the present findings (using dipyridamole stress) and those of Follansbee et al. (using exercise stress) may reflect racial differences or differences in the backgrounds of the patients. The frequency of diffuse sclerosis was not significantly different between the patients who were judged to be positive in the dipyridamole Tl-201 perfusion scan and those who were judged to be negative. In line with those findings, we did not find any relationship between the severity of skin sclerosis and the presence of heart abnormalities. However, our failure to find a significant relationship between muscle involvement and myocardial involvement in SSc contradicts previous studies describing an association between myositis and myocarditis in SSc patients.[26–28] It is suggested that this contradiction stems more from the limited sample size in the present study than from any real difference in outcome.

The usefulness of stress myocardial perfusion scans has been reported for other systemic rheumatic diseases. Exercise Tl-201 myocardial perfusion scans have been used for younger (below 50 years) systemic lupus erythematosus patients and children,[29,30] and dipyridamole Tl-201 perfusion scans have been used for rheumatoid arthritis patients.[31] The findings of these studies showed that asymptomatic myocardial perfusion abnormalities occurred, and were more common than was previously suspected.

Recently, Steen et al.[32] reported the usefulness of an exercise thallium scintigram as a prognostic factor to assess myocardial involvement in SSc. In a follow-up evaluation of 48 unselected SSc patients, those with larger perfusion defects as detected by an exercise thallium scintigram had a significantly increased risk of developing cardiac events or death. The size of the initial defect was the best predictor of later adverse events. These researchers used maximal exercise by treadmill as the stress to detect myocardial involvement. Therefore, the application of dipyridamole instead of exercise to Tl-201 scintigraphy may be especially beneficial to evaluate possible cardiac involvement in SSc patients; dipyridamole thallium-201 perfusion scanning may serve this purpose.

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