Cardiac Magnetic Resonance Imaging with Pharmacological Stress Perfusion and Delayed Enhancement in Asymptomatic Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To assess cardiac involvement in asymptomatic patients with systemic sclerosis (SSc) by cardiac magnetic resonance imaging (MRI).

Methods. Ten asymptomatic patients with SSc (all female; mean age 59.5 ± 9.4 yrs) underwent contrast enhanced cardiac MRI on a 1.5 T MRI device. Adenosine triphosphate was used for stress and rest perfusion to assess perfusion defects due to microvascular impairment or ischemia, and delayed enhanced (DE) imaging was obtained for the assessment of myocardial necrosis and fibrosis. We evaluated the pathophysiological associations of stress perfusion combined with DE imaging with SSc disease severity measures.

Results. Stress perfusion defects were seen in 5 out of 9 patients (56%): 4 had nonsegmental subendocardial perfusion defects and one had a segmental subendocardial perfusion defect. Three patients were found to have DE. DE was not observed in any patient without perfusion defect; and among the 5 patients with perfusion defects, 3 (60%) had DE. Two of the 3 had DE in segments not matching the region of nonsegmental perfusion defects. The remaining one had a segmental subendocardial DE matching the region of a segmental perfusion defect. Perfusion defects were seen in 75% of patients with a history of digital ulceration compared to only 20% of those without history of ulceration.

Conclusion. Subclinical myocardial involvement, as detected by cardiac MRI, was frequent in asymptomatic patients with SSc. Cardiac MRI may aid in understanding the pathophysiological mechanism of SSc. (First Release Dec 1 2008; J Rheumatol 2009;36:106–12; doi:10.3899/jrheum.080377)

Key Indexing Terms:
CARDIAC MAGNETIC RESONANCE IMAGING DELAYED ENHANCEMENT
PHARMACOLOGICAL STRESS PERFUSION
ASYMPTOMATIC PATIENTS SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a connective tissue disease clinically characterized by widespread vascular lesions and fibrosis of the skin and major organs including lungs, kidneys, and heart. Pathological studies have revealed that fibrosis can occur in any part of the heart, and appears to be present in 12%–80% of autopsy studies[1,2]. Cardiac involvement is often clinically silent[3], and is recognized as a poor prognostic factor. Ferri, *et al*[4] showed that in a cohort of 1012 Italian patients, 35% had cardiac symptoms, and cardiac involvement alone accounted for 36% of deaths. Given this, the early detection of cardiac involvement may play a vital role in identifying patients at the greatest risk of cardiac-related morbidity and mortality. Although noninvasive methods, such as single-photon emission computed tomography (SPECT) and echocardiography, may reveal functional abnormalities[5-7], spatial resolution is not of sufficient sensitivity, objectivity, or reproducibility to identify myocardial involvement.

Contrast-enhanced cardiac magnetic resonance imaging (MRI) is recognized as a valuable tool for the diagnosis of myocardial diseases. Stress and rest perfusion MRI can be used to identify myocardial ischemia in various kinds of car-

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diomyopathy as well as ischemic heart disease. Nonsegmental perfusion defects (PD) not corresponding to any epicardial coronary artery distribution, are highly suggestive of microvascular impairment, as reported in patients with small-vessel diseases such as Syndrome X[8,9], while segmental defects correspond to macrovascular (epicardial artery) impairment. Areas showing delayed enhancement (DE) correspond to zones of myocyte necrosis or myocardial fibrosis as shown by comparison with histopathology[10]. Accordingly, combining stress perfusion and DE MRI could be useful to evaluate cardiac involvement more accurately than each approach separately. Studies[11,12] of cardiac MRI in SSc have investigated only rest perfusion or DE MRI alone. Combining perfusion and DE MRI together may reveal important clues to the pathophysiologic mechanisms of cardiac involvement in SSc.

We used stress and rest perfusion and DE MRI to evaluate cardiac involvement in SSc patients with no cardiac symptoms.

METHODS AND MATERIALS

Patients. Consecutive female patients with SSc as defined by the American Rheumatism Association classification criteria[13] were recruited from the outpatient rheumatology clinic at Itabashi Chuo Medical Center, Tokyo, between December 2005 and March 2007. We chose to include only women to avoid the potential confounding effect of gender in this small pilot study. Other inclusion criteria were absence of a history of or current treatment with prednisone. Exclusion criteria were pregnancy, evidence of cardiomegaly on chest radiograph, symptoms of heart failure, coronary artery disease (angina and/or electrocardiographic signs of myocardial ischemia), systolic blood pressure < 90 or > 150 mm Hg, heart rate < 50 or > 130 bpm, pulmonary arterial hypertension (systolic arterial pressure > 40 mm Hg determined by echocardiography), severe valvular heart disease, atrial fibrillation, diabetes mellitus, hyperlipidemia, dyslipidemia, past and current history of smoking, inadequate echocardiogram, history of bronchoconstriction, contraindication to MRI, hypersensivity to gadolinium or adenosine triphosphate (ATP), and past or current treatment with prostacyclin for digital ulceration. Informed consent was obtained from all patients and the study was approved by the ethics committee of Itabashi Chuo Medical Center.

Assessments. All patients underwent a standardized history and physical examination, routine laboratory investigations, antitopoisomerase and anticentromere antibody tests, and basic screening for conventional atherosclerotic disease risk factors, including cigarette smoking, systolic and diastolic blood pressure measurement, serum cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), fasting blood glucose concentration, chest radiograph, a 12-lead electrocardiogram (ECG) and transthoracic echocardiography at study entry. We estimated Framingham 10-year hard cardiovascular risk[14] in all patients.

MRI scanning. Patients underwent cine-MRI, pharmacological stress and rest perfusion, and DE MRI (Figure 1). All contrast MR studies were performed with a 1.5 T MRI machine (Achieva, Philips, The Netherlands). ATP was infused using an automated power injector at a constant rate of 0.16 mg/kg body weight per minute for 5 minutes as a pharmacological stress agent[15,16]. Subsequently, a gadolinium-based contrast agent (Gd-DTPA; Magnevist, Schering AG, Berlin, Germany) was injected into the right antecubital vein (0.1 mmol/kg body weight) during a first-pass perfusion sequence using an IR balanced Turbo Field Echo sequence (TR 2.8 ms, TE 1.38 ms, FA 45, slice thickness 8 mm, preparation pulse delay 200 ms), and images in 4 contiguous short-axis orientations were acquired at every 2 heartbeats. ATP infusion was stopped after completion of the sequence. After 5 minutes of stress perfusion MRI, rest first-pass perfusion was scanned by the same sequence and same injection protocol for the gadolinium contrast agent. After a 10-minute delay from last-perfusion MRI, DE imaging was obtained using a 3D-Turbo field echo sequence (TR 5.1 ms, TE 2.5 ms, FA 15, slice thickness 8 mm).

MRI interpretation. Imaging was viewed and analyzed independently by 2 radiologists and one rheumatologist who were blinded to clinical information. Stress PD lesions, when present, were characterized by distribution as segmental or nonsegmental. DE lesions, when present, were characterized by distribution as nodular, linear, or diffuse. The pathological MRI findings were interpreted according to the algorithm in Figure 2, and are categorized in Table 1. Nonsegmental PD with DE indicated microvascular impairment with fibrosis. Nonsegmental PD without DE indicated microvascular impairment without fibrosis. Segmental PD with matched DE indicated macrovascular impairment with necrosis (i.e., myocardial infarction; MI).

RESULTS

Characteristics of the 10 enrolled patients are summarized in Table 2. Patients had a mean age of 59.5 ± 9.4 years at the time of scanning and a mean SSc disease duration of 4.6 ± 3.9 years. According to the extent of cutaneous involvement, half had diffuse cutaneous SSc and the remaining half had limited cutaneous SSc. Mean total skin score was 10.7 ± 3.7.

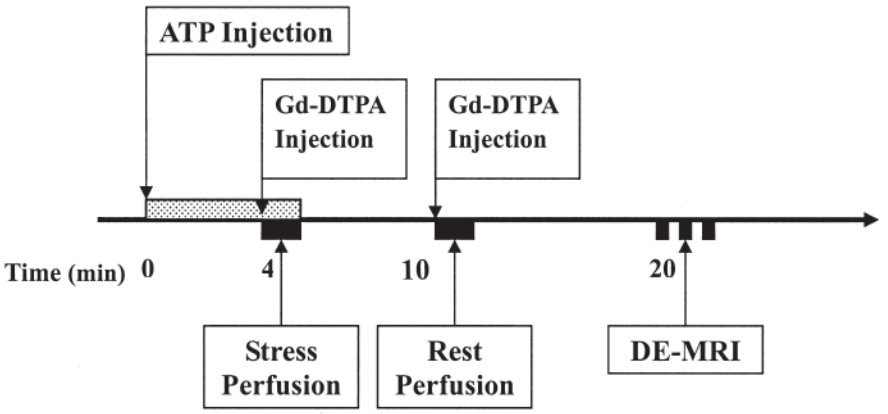

Figure 1. Timeline of the MRI imaging procedure. ATP: adenosine triphosphate, DE: delayed enhancement, Gd-DPTA: gadolinium contrast agent.

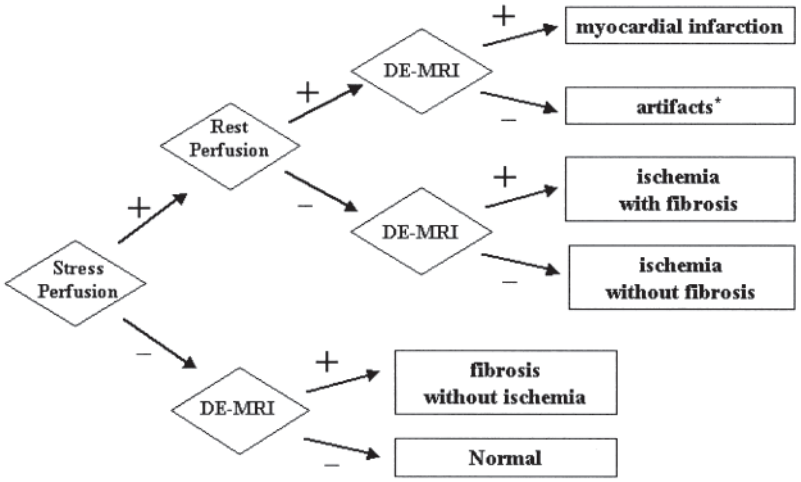

Figure 2. The interpretation algorithm is based on 2 principles. First, with stress and rest perfusion MRI, we have complementary methods to obtain information on the presence or absence of ischemia or myocardial infarction (MI). Second, with perfusion MRI and delayed enhancement (DE)-MRI, we have independent methods to obtain information on the presence or absence of MI or fibrosis. DE-MRI should be more accurate for the diagnosis of MI and fibrosis. Perfusion defects that have similar intensity and extent during both stress and rest but do not have infarction on DE-MRI are artifacts.

Table 1. Interpretation based on stress and rest perfusion and delayed enhancement (DE) MRI.

Stress Perfusion	Rest Perfusion	Delayed Enhancement	Pathophysiological Implication
Nonsegmental PD+	PD–	DE+	Microvascular impairment with fibrosis
Nonsegmental PD+	PD–	DE–	Microvascular impairment without fibrosis
Segmental PD+	PD–	DE–	Macrovascular impairment
Segmental PD+	Matched PD+	Matched DE+	Myocardial infarction

PD: perfusion defect.

All patients had Raynaud's phenomenon, but only 4 (40%) had a history of digital ulceration with evidence of digital pitting scars on examination. Five patients (50%) had interstitial lung disease, but none had pulmonary hilar enlargement, cardiomyopathy, or pulmonary edema on radiograph. According to the exclusion criteria, none had pulmonary hypertension. Five patients (50%) had esophageal involvement, but none had kidney involvement. On average, cardiovascular risk was low for the group, with patients demonstrating no ECG abnormalities, normal left-ventricular chamber dimensions and systolic function on ECG, and generally low traditional cardiovascular risk factors, with a mean Framingham 10-year hard cardiovascular risk score of 4% ± 2%.

Myocardial perfusion by MRI. Contrast-enhanced cardiac MRI was successfully completed in 9 of the 10 patients. Stress and rest perfusion were canceled because of ATP-induced dyspnea in one patient (Patient 10). The results of stress and rest perfusion scanning are shown in Table 3. PD during pharmacological stress were seen in 5 of the 9 patients (56%) who successfully completed stress perfusion. Of these, 4 (80%) demonstrated circumferential (nonsegmental) PD suggestive of diffuse subendocardial microvascular impairment, while the remaining one (20%) had segmental subendocardial defects.

Myocardial enhancement by MRI and association with perfusion defects. Among the 9 patients who completed the perfusion portion of the imaging protocol, 3 (33%) were found to have DE (diffuse in one and focal in 2). Importantly, DE was not observed in any patient without PD, and among the 5 patients with PD, 3 (60%) demonstrated DE. Two of the 3 had DE in segments not matching the region of nonsegmental PD, suggesting myocardial fibrosis (Figures 3 and 4). The remaining patient with both PD and DE showed segmental subendocardial DE matching the same region of a segmental subendocardial PD (Figure 5). This pattern is commonly observed in patients with subendocardial MI. After cardiac MRI scanning, one patient with nonsegmental PD and diffuse DE underwent coronary CT angiography, which showed no coronary abnormalities.

Association of cardiac MRI findings with clinical characteristics of SSc. Associations between MRI findings and clinical characteristics of SSc are summarized in Table 4. No clinical characteristic was associated with any MRI finding with the possible exception of digital ulceration, in which PD were seen in 75% (3 of 4) of the patients compared to

Table 2. Clinical and laboratory characteristics of patients with SSc (n = 10).

Characteristic	
Age, yrs	59.5 ± 9.4
Female, n (%)	10 (100)
Cutaneous subtype, diffuse:limited, n (%)	5 (50):5 (50)
Total skin score	10.7 ± 3.7
Disease duration, yrs	4.6 ± 3.9
History of digital ulcer (including pitting scar), n (%)	4 (40)
Interstitial lung disease, n (%)	5 (50)
Esophageal involvement, n (%)	5 (50)
Framingham 10-year hard cardiovascular risk, %	3.9 ± 2.2
Fasting plasma sugar, mg/dl	93 ± 5.6
Systolic blood pressure, mm Hg	134 ± 7.5
Diastolic blood pressure, mm Hg	78 ± 6.8
Smoking (ever and current), n (%)	0 (0)
Total cholesterol, mg/dl	180 ± 11.4
Triglycerides, mg/dl	130 ± 9.4
High-density lipoprotein, mg/dl	50 ± 6.4
Low-density lipoprotein, mg/dl	104 ± 11.1
Antitopoisomerase I antibodies, n (%)	5 (50)
Anticentromere antibodies, n (%)	2 (20)
Normal ECG: Q wave (–), arrhythmia (–), block (–), n (%)	10 (100%)
Ejection fraction on ECE, %	68 ± 3.7

Except where indicated otherwise, values are mean ± SD. ECG: electrocardiography.

only 20% (1 of 5) of those without this history (prevalence ratio 3.75). However, owing to the small overall number of patients in the study, this association was not statistically significant.

DISCUSSION

In this pilot study, we used cardiac MRI to assess myocardial involvement in SSc patients with no cardiac symptoms. To our knowledge this is the first investigation to combine both perfusion and delayed enhancement cardiac MRI for assessing cardiac involvement in such patients. Our preliminary data lend support for a high prevalence of microvascular impairment in the myocardia of patients with SSc, and a high prevalence of myocardial enhancement, representing fibrosis, in those with microvascular involvement.

Clinical diagnosis of myocardial involvement in SSc remains problematic. Myocardial biopsy may increase the frequency of detection of the disease but is limited by its invasive nature and relatively low diagnostic yield compared with that of autopsy[17,18]. Thus, various noninvasive methods have been used in an effort to reveal cardiac abnormalities.

SPECT has been used in a number of studies to assess myocardial perfusion in SSc and several investigators have reported that myocardial perfusion was reduced in symptomatic patients with SSc[19]. Recently, Lin, *et al*[20] reported that PD were seen in 24% of patients with asymptomatic SSc. Although myocardial perfusion SPECT is widely used in clinical practice and the high sensitivity of SPECT in myocardial perfusion has been reported, the spatial resolution of this modality is limited. Ishida, *et al*[21] reported that pharmacological stress perfusion MRI is superior to SPECT for the assessment of myocardial ischemia.

The most common clinical imaging in patients with suspected heart disease is conventional echocardiography, which is rapid, noninvasive, and routinely available for assessment of systolic and diastolic dysfunction. On the other hand, cardiac MRI can provide information about myocardial perfusion. In the "ischemic cascade" of ischemic heart disease, hypoperfusion will lead first to diastolic and then to systolic ventricular dysfunction[22]. We considered that cardiac MRI would have the potential to make a diagnosis of cardiac involvement in SSc earlier than echocardiography, since it enables dynamic first-pass perfusion MRI of the entire left-ventricular myocardium, with improved imaging quality and higher spatial resolution. Pharmacological stress perfusion MRI has been shown to be an accurate method for detecting coronary artery disease[23]. Klem, *et al*[24] have reported that the addition of delayed enhancement MRI to the stress/rest perfusion examination would help distinguish true perfusion defects from artifact, and improve test reliability to the point that rapid visual interpretation could be performed with high accuracy. Moreover, combining stress/rest perfusion and delayed enhancement MRI is an accurate method for detecting myocardial abnormalities[25,26].

Table 3. Pattern classification based on perfusion and delayed enhancement (DE) MRI.

Patient	Digital Ulcer	Stress Perfusion	Rest Perfusion	DE
1	+	Nonsegmental PD (circumferential)	PD–	Diffuse patchy DE
2	–	Nonsegmental PD (circumferential)	PD–	Focal small DE in intermediate layer
3	+	Nonsegmental PD	PD–	DE–
4	+	Nonsegmental PD (circumferential)	PD–	DE–
5	–	Segmental subendocardial PD	Segmental subendocardial PD	Segmental subendocardial PD
6	+	PD–	PD–	DE–
7	–	PD–	PD–	DE–
8	–	PD–	PD–	DE–
9	–	PD–	PD–	DE–
10	–	NA (dyspnea)	NA	Linear DE in intermediate layer

PD: perfusion defect, NA: not assessable.

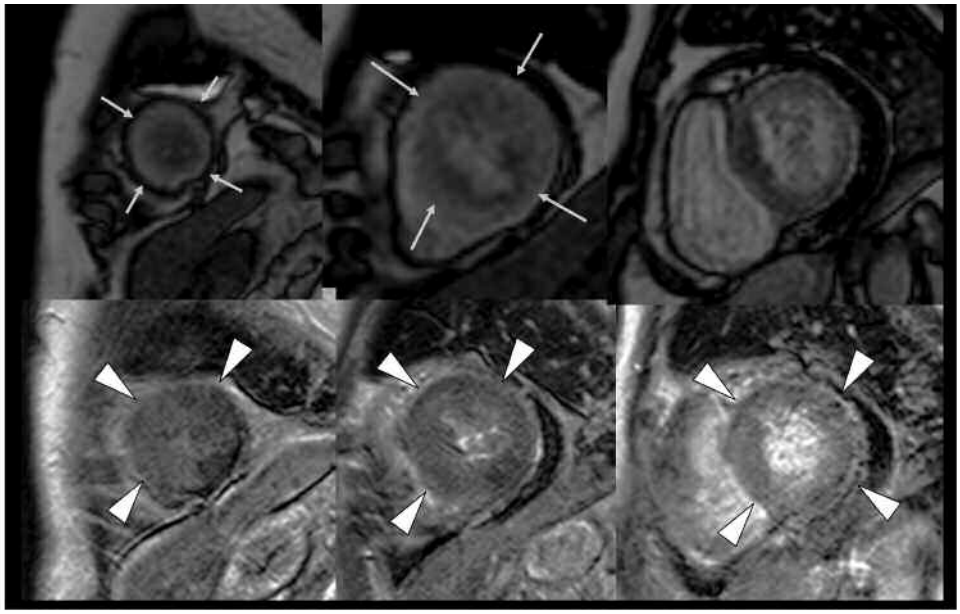

Figure 3. This case shows nonsegmental perfusion defect with diffuse delayed enhancement. A. Stress perfusion MRI shows circumferential subendocardial perfusion defect (arrows). B. Delayed enhanced imaging shows diffuse and faint enhancement (arrowheads).

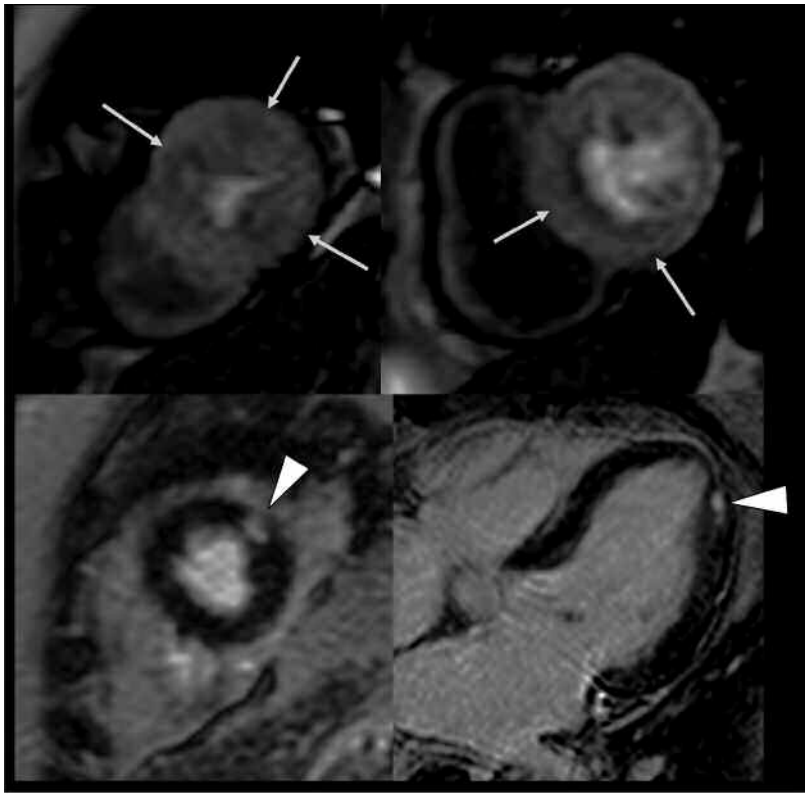

Figure 4. This case shows nonsegmental perfusion defect with segmental delayed enhancement. A. Stress perfusion MRI shows nonsegmental perfusion defect (arrows). B. Delayed enhanced imaging shows small focal enhancement (arrowheads) in intermediate layer.

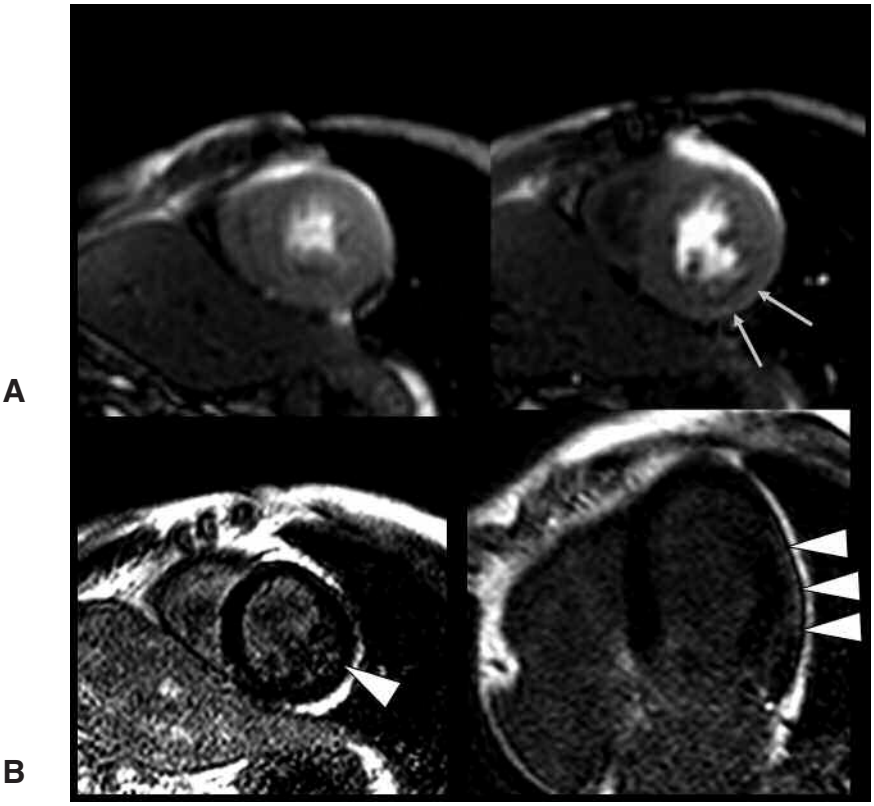

Figure 5. This case shows segmental perfusion defect with segmental delayed enhancement. A. Stress perfusion MRI shows segmental perfusion defect (arrows). B. Delayed enhanced imaging shows segmental enhancement (arrowheads) in subendocardial and intermediate layer.

Table 4. Clinical characteristics as a function of perfusion defect (PD).

Characteristic	PD+, n = 5	PD–, n = 4	DE+, n = 4	DE–, n = 6
Age, yrs	65.2	52.8	65.8	55.5
SSc type, diffuse:limited	3:2	1:3	3:1	2:4
SSc duration, yrs	4.6	6.5	5.0	5.5
Scl-70 (%)	3 (60)	2 (50)	3 (75)	2 (33)
ACA (%)	1 (20)	1 (25)	1 (25)	1 (17)
Digital ulcer (%)	3 (60)	1 (25)	1 (25)	3 (50)

DE: delayed enhancement, Scl-70: antitopoisomerase I antibodies, ACA: anticentromere antibodies.

Our results that DE was seen only where PD are present indicated the interpretation of myocardial fibrosis with microvascular impairment. The cause of cardiac involvement in SSc is unknown, but our results might support the hypothesis that microvascular impairment is involved in the pathophysiology, leading to fibrosis[27].

Myocardial fibrosis (manifested by DE on MRI) is the hallmark of cardiac involvement in SSc, but myocardial fibrosis may be also seen following MI. In our study and those of other investigators, myocardial fibrosis generally did not correspond to the regional distribution of a single coronary artery[1,28], indicating that fibrosis was not due to myocardial infarction. In one patient, however, DE was found to be mapped to the territory of a single coronary artery, strongly suggesting prior subendocardial MI. Tarek, *et al*[29] have studied coronary angiographic findings in patients with asymptomatic SSc. They indicated that the higher incidence of coronary angiographic abnormalities and coronary artery vasculopathy secondary to SSc is more common than previously thought. Insofar as asymptomatic coronary artery disease is a risk factor for subsequent MI, it may be prudent to consider cardiac evaluation even in patients with asymptomatic SSc.

Interestingly, in 3 of our patients, we observed an association between a history of digital ulcer caused by vasospasm and MRI findings of microvascular impairment. Persistent vasospasm is a contributing factor to vasculopathy in patients with SSc, leading to ischemic tissue damage of distal digits, and development of digital ulceration or gangrene. Our findings could suggest a common pathophysiological mechanism for myocardial abnormalities and digital ischemia in SSc.

Our study has limitations. This was a pilot study and sample size was insufficient to make firm conclusions. In addition, we did not include a healthy control group, so we cannot assert that our findings are unique to patients with SSc. Although we excluded cardiovascular disease by symp-

toms, ECG, and echocardiography, the MRI studies in one patient nonetheless suggested a prior MI. Thus, MRI might be argued to be a more useful method than ECG for detecting silent MI.

These preliminary findings suggest that cardiac MRI can be promoted as a tool to assess myocardial pathology in SSc, and to further elucidate the pathophysiology of SSc. Enhancing the early recognition of cardiac involvement in patients with asymptomatic SSc by MRI may be clinically relevant in that it might assist in treating these patients, prompt closer monitoring for cardiovascular signs and symptoms, and permit earlier intervention.

To our knowledge, our study is the largest patient series to date to report cardiac abnormalities using combined pharmacological stress and rest and delayed enhancement MRI. Cardiac involvement is common in SSc. Its detection and histological confirmation are often difficult because of a lack of symptoms. Thus, cardiac MRI might be considered a useful and less invasive diagnostic method for assessing cardiac involvement in asymptomatic patients with SSc. Further studies of this diagnostic tool should be evaluated to discuss its utility.

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