Detection of Left Ventricular Regional Dysfunction and Myocardial Abnormalities Using Complementary Cardiac Magnetic Resonance Imaging in Patients with Systemic Sclerosis without Cardiac Symptoms: A Pilot Study

Yasuyuki Kobayashi\(^1\), Hitomi Kobayashi\(^2\), Jon T Giles\(^3\), Isamu Yokoe\(^4\), Masaharu Hirano\(^5\), Yasuo Nakajima\(^1\) and Masami Takei\(^2\)

**Abstract**

**Objective** We sought to detect the presence of left ventricular regional dysfunction and myocardial abnormalities in systemic sclerosis (SSc) patients without cardiac symptoms using a complementary cardiac magnetic resonance (CMR) imaging approach.

**Methods** Consecutive patients with SSc without cardiac symptoms and healthy controls underwent CMR on a 1.5 T scanner. The peak systolic regional function in the circumferential and radial strain (Ecc, % and Err, %) were calculated using a feature tracking analysis on the mid-left ventricular slices obtained with cine MRI. In addition, we investigated the myocardial characteristics by contrast MRI. Pharmacological stress and rest perfusion scans were performed to assess perfusion defect (PD) due to micro- or macrovascular impairment, and late gadolinium enhancement (LGE) images were obtained for the assessment of myocarditis and/or fibrosis.

**Results** We compared 15 SSc patients with 10 healthy controls. No statistically significant differences were observed in the baseline characteristics between the patients and healthy controls. The mean peak Err and Ecc of all segments was significantly lower in the patients than the controls (p=0.011 and p=0.003, respectively). Four patients with LGE (28.6%) and seven patients with PD (50.0%) were observed. PD was significantly associated with digital ulcers (p=0.005). Utilizing a linear regression model, the presence of myocardial LGE was significantly associated with the peak Ecc (p=0.024). After adjusting for age, the association between myocardial LGE and the peak Ecc was strengthened.

**Conclusion** A subclinical myocardial involvement, as detected by CMR, was prevalent in the SSc patients without cardiac symptoms. Regional dysfunction might predict the myocardial abnormalities observed in SSc patients without cardiac symptoms.

**Key words:** cardiac magnetic resonance imaging, LV regional dysfunction, myocardial abnormalities, systemic sclerosis

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**Introduction**

In patients with systemic sclerosis (SSc), myocardial involvement is common, may have serious consequences, and may lead to a poor prognosis (1). The regional left ventricular (LV) dysfunction reflects the myocardial involvement (2). LV dysfunction may arise from a number of distinct processes, including micro- and macrovascular coronary ischemia, myocardial inflammation (myocarditis), and/...
or myocardial fibrosis, any of which may occur in SSc. A regional dysfunction may be observed with cardiac magnetic resonance (CMR) imaging prior to myocarditis, myocardial fibrosis or myocardial infarction, electrocardiogram (ECG) abnormalities and chest pain. Therefore, strain measurement by CMR may be a method that is more sensitive to assess the early myocardial involvement in SSc. Therefore, CMR provides a highly accurate and sensitive method for evaluating the changes in the regional ventricular function (3). The regional LV function in SSc has not yet been systematically studied using CMR imaging.

Conversely, using perfusion and late gadolinium enhancement (LGE) imaging with CMR may reveal important clues to the pathophysiologic mechanisms underlying the myocardial characteristics in SSc. In this study, we aim to detect the LV regional dysfunction and myocardial abnormalities in patients with SSc without cardiac symptoms using a complementary CMR approach with cine MRI, perfusion and late gadolinium enhancement.

Materials and Methods

Consecutive patients with SSc as defined by the American Rheumatism Association classification criteria (4) were recruited from the outpatient rheumatology clinic at Itabashi Chuo Medical Center between September 2011 and December 2013; healthy volunteers were included in the study as the control group. SSc patients and control subjects with no history and/or clinical findings of systemic and pulmonary arterial hypertension, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, dyslipidemia, or echocardiographic abnormalities underwent a complementary CMR on a 1.5T MRI scanner (Achieva, Philips, Amsterdam, The Netherlands) with steady-state free precession (SSFP) cine MRI, pharmacological stress and rest perfusion, and delayed enhancement MRI. The peak regional radial and circumferential strain (Err, % and Ecc, %) of the left ventricle in the middle-cavity on the short axis [based on the American Heart Association (AHA) 16-segments model] were calculated by feature tracking (TOMTEC, Unterschleissheim, Germany) using cine MRI. A strain analysis is superior to a visual analysis of the wall motion for detecting differences in the myocardial deformation and determining the timing of the contraction. Strain measurements are expressed as the fractional change in the length (as a percentage) from the resting state (end diastole) to the state following the myocardial contraction (5). CMR with feature tracking on cine MRI has been developed in order to meet the clinical need for a fast and quantitative assessment of the myocardial segmental strain analysis (Fig. 1) (6, 7). Pharmacological stress and rest perfusion MRI can be used to identify myocardial ischemia in various kinds of cardiomyopathy as well as ischemic heart disease (8). Non-segmental perfusion defects (PD) not corresponding to any epicardial coronary artery distribution are highly suggestive of a microvascular impairment, as reported in patients with small-vessel diseases such as syndrome X, while segmental defects correspond to a macrovascular (epicardial artery) impairment. The areas which demonstrate LGE correspond to the zones of myocardial necrosis, fibrosis or myocarditis as shown by comparison with histopathology (9). We compared the prevalence of CMR abnormalities between the patients and controls and explored possible associations between the CMR abnormalities and the disease characteristics of SSc. The study was approved by the local ethics committee (Itabashi Chuo Medical Center, Japan), and informed consent...
was obtained from each patient in accordance with the Helsinki Declaration of 1975 (revised in 1983).

**Statistical analysis**

Group comparisons were made using the Wilcoxon rank sum test and Fisher’s exact test, where appropriate. Single and multivariable linear regression analyses were used to assess the association between the peak Ecc/Err and the disease characteristics. Statistical calculations were performed using the JMP 9 software package (SAS Institute, Cary, USA). Statistical significance was considered to exist at p<0.05.

**Results**

We compared 15 patients with SSc (100% women; mean age, 59.5±9.0 years; 8 had limited cutaneous SSc and 7 had diffuse cutaneous SSc) with 10 healthy controls (100% women; mean age, 55.7±4.5 years). No statistically significant differences were observed in the baseline characteristics between the patients and the healthy controls (Table 1). The mean peak Ecc and Err of all segments were significantly reduced in the SSc patients than in the controls (p=0.011 and p=0.003, respectively) (Fig. 2a). The mean peak Ecc and Err were not significant (p=0.076 and p=0.054, respectively) (Fig. 2c). The mean peak Ecc and Err in the patients with PD tended to be reduced compared to those without PD, however, this difference was not significant (p=0.259 and p=0.535, respectively) (Fig. 2d). PD was strongly and significantly associated with digital ulcers, as all of the patients with digital ulcers exhibited PD (p=0.005) (Table 2). Utilizing a linear regression model, the presence of myocardial LGE was significantly associated with the peak Ecc (p=0.024) (Table 3). After adjusting for confounding by age, the association between the myocardial LGE and the peak Ecc was strengthened.; specifically, the group with myocardial LGE demonstrated a mean peak Ecc approximately 3.62 units lower than the group without LGE. Additional adjustment for the cutaneous type of SSc and the Framingham risk score did not modify the association of LGE with the mean peak Ecc. The myocardial LGE and age accounted for almost half of the total variability in peak Ecc (R² = 0.42).

**Discussion**

In this pilot study, we used CMR to assess the myocardial regional dysfunction and pathological abnormalities in SSc patients with no cardiac symptoms. This is the first investigation demonstrating that the regional function in circumferential and radial strain was impaired in SSc patients with no clinical evidence of cardiovascular disease and the regional dysfunction may be associated with myocardial characteris-

### Table 1. No Statistically Significant Differences Were Observed in Baseline Characteristics between the Patients and Healthy Controls.

<table>
<thead>
<tr>
<th></th>
<th>SSc (n=15)</th>
<th>SSc (n=15)</th>
<th>Controls(n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diffuse</td>
<td>Localized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years†</td>
<td>59.5±9.0</td>
<td>59.4±8.3</td>
<td>59.5±10.2</td>
<td>0.22*</td>
</tr>
<tr>
<td>Sex</td>
<td>0 M / 15 F</td>
<td>0 M / 7 F</td>
<td>0 M / 8 F</td>
<td>1.00**</td>
</tr>
<tr>
<td>Framingham 10 years score</td>
<td>2.2</td>
<td>2.1</td>
<td>2.3</td>
<td>0.86*</td>
</tr>
<tr>
<td>Disease Duration, years †</td>
<td>4.8±3.1</td>
<td>5.0±3.1</td>
<td>4.7±5.1</td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction (Echo), %†</td>
<td>64.5±1.4</td>
<td>66.5±1.4</td>
<td>64.5±3.4</td>
<td></td>
</tr>
<tr>
<td>Total skin thickness score†</td>
<td>12.0±5.8</td>
<td>14.3±6.8</td>
<td>10.0±2.8</td>
<td></td>
</tr>
<tr>
<td>Diffuse or limited</td>
<td>7:8</td>
<td>7:6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Digital ulcer</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Antitopoisoenerase I antibodies, n</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anticentromere antibodies, n</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>DLCO, %</td>
<td>59.0±12.5</td>
<td>58.0±12.5</td>
<td>59.0±2.5</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Involvement</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Current Treatment:</td>
<td>Calcium Channel Inhibitor, n</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin Analog, n</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*: Wilcoxon rank sum test between SSc and Controls
**: Fisher’s exact test between SSc and Controls
micro- and macrovascular coronary ischemia, myocardial dysfunction may arise from a number of distinct processes, including myocardial characteristics (14). The regional dysfunction and radial strain and for the evaluation of the presence of the global and regional cardiac function in circumferential and radial strain and disease characteristics. 

Pathological studies have revealed that fibrosis may occur in any region of the heart and appears to be present in 12-80% of autopsy studies (10, 11). The myocardial involvement is often clinically silent (12) and it is also recognized as a poor prognostic factor. As a result, the early detection of myocardial involvement may play a vital role in identifying patients at the greatest risk of cardiac-related morbidity and mortality, thus allowing for earlier treatment. We previously demonstrated that a subclinical myocardial involvement, as detected by combined pharmacological perfusion and late gadolinium enhancement MRI, was frequent in SSc patients without cardiac symptoms (13). In the present investigation, we confirmed these findings with a larger sample size and, importantly, evaluated the regional function in the circumferential and radial strain and disease characteristics.

CMR has recently been employed for the surveillance of the global and regional cardiac function in circumferential and radial strain and for the evaluation of the presence of myocardial characteristics (14). The regional dysfunction may arise from a number of distinct processes, including micro- and macrovascular coronary ischemia, myocardial inflammation (myocarditis), and/or myocardial fibrosis (15). We considered that combining the regional function with perfusion and late gadolinium enhancement MRI may be an accurate method for detecting early myocardial abnormalities in SSc patients.

Interestingly, our results demonstrated that the regional function may contribute to the change in the myocardial characteristics in the absence of cardiac symptoms. Previous studies utilizing CMR indicated a potential relationship between LGE and the regional function (16, 17). Although the disease state was different among these studies, our data may support these findings; therefore, the regional dysfunction may predict myocardial abnormalities in SSc patients without cardiac symptoms.

Our preliminary data lend support for a high prevalence of regional dysfunction in patients with both the diffuse and limited cutaneous types of SSc compared with the control subjects.

Furthermore, we observed an association between digital ulcers, presumably caused by chronic vasospasm and/or microvascular remodeling, and the CMR findings of microvascular impairment. Thus, our results may suggest a common pathophysiological mechanism for the myocardial abnor-
The high detectability and reliability of the measurements obtained by CMR indicates that CMR is a promising clinical tool for the detection of early myocardial involvement in SSc. As a result, we may select SSc patients who may benefit from more aggressive therapies thereby contributing to the improvement in the patient’s outcomes.

There are some limitations associated with this study. This was a pilot study and the sample size was too small for definitive conclusions. The lack of non-SSc controls in the perfusion defect and late gadolinium enhancement limits our ability to conclude that our findings are unique to SSc patients; however, the much higher frequency of myocardial abnormalities observed in the present study compared with studies conducted in non-SSc patients with similar demographic characteristics and cardiovascular disease (CVD) risk factors is suggestive of a true disease effect.

## Conclusion

Subclinical myocardial involvement, as detected by CMR, was prevalent in the SSc patients without cardiac symptoms. An evaluation with CMR therefore appears to be useful in detecting subclinical myocardial involvements in SSc. The

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**Figure 3.** Perfusion defect and late gadolinium enhancement. a: Rest perfusion: No perfusion defect was noted in myocardium. b: Stress perfusion: Perfusion defect was seen in anterior, lateral and inferior myocardium (arrows). c, d: Late gadolinium enhancement: Focal late enhancement was noted in apical region (arrows).

**Table 2.** Digital Ulcer and Perfusion Defect. PD Was Strongly and Significantly Associated with Digital Ulcer, as All of the Patients with Digital Ulceration Exhibited PD (p=0.005).

<table>
<thead>
<tr>
<th>Digital Ulcer (+)</th>
<th>Digital Ulcer (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion Defect (+)</td>
<td>6</td>
</tr>
<tr>
<td>Perfusion Defect (-)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
</tr>
</tbody>
</table>

Fisher’s exact test p=0.005
The authors state that they have no Conflict of Interest (COI).

References


16. Hoffmann R, Altiek E, Friedman Z, et al. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography in comparison to late gadolinium enhancement cardiac magnetic

Table 3. Linear Regression Analysis in Ecc and Err.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1 β</th>
<th>Model 2 β</th>
<th>Model 3 β</th>
<th>Model 4 β</th>
<th>Model 5 β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Gd Enhancement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age**</td>
<td>-0.15</td>
<td>0.280</td>
<td>-0.15</td>
<td>0.280</td>
<td>-0.15</td>
</tr>
<tr>
<td>Cutaneous type, diffuse</td>
<td>-0.94</td>
<td>0.465</td>
<td>-0.94</td>
<td>0.465</td>
<td>-0.94</td>
</tr>
<tr>
<td>Framingham score**</td>
<td>-0.47</td>
<td>0.700</td>
<td>-0.47</td>
<td>0.700</td>
<td>-0.47</td>
</tr>
<tr>
<td>Perfusion Defect*</td>
<td>-1.00</td>
<td>0.460</td>
<td>-1.00</td>
<td>0.460</td>
<td>-1.00</td>
</tr>
</tbody>
</table>

R²***: 0.36, 0.42, 0.39, 0.37, 0.39

*β coefficient represent the average change in the outcome for those with the characteristic vs. those without.

**β coefficient represent the average change in the outcome per 1 unit increase in the characteristic.

***R² is the percentage of the total variability in the outcome explained by the aggregate of the predictors in the model.

regional dysfunction may predict myocardial abnormalities in SSc without cardiac symptoms. Our findings may suggest a pathophysiological mechanism to explain the relationship between myocardial abnormalities and digital ischemia in SSc.


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