To assess early cardiac involvement and clinical utility of dipirydamole stress Cardiac Magnetic Resonance Imaging (CMRI) in asymptomatic patients with Systemic Sclerosis (SSc)

Poster No.: C-1150
Congress: ECR 2011
Type: Scientific Exhibit
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Keywords: Cardiac, Cardiovascular system, MR, Contrast agent-intravenous, Pathology
DOI: 10.1594/ecr2011/C-1150
Purpose

The aim of this study is to assess the clinical utility of pharmacological stress and rest perfusion cardiac magnetic resonance imaging (CMRI), in asymptomatic patients with SSc.

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 cardiomyopathy as well as ischemic heart disease. Non-segmental 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, while segmental defects correspond to macrovascular (epicardial artery) impairment. Studies of cardiac MRI in SSc have investigated only rest perfusion or DE MRI alone. In our experience we use stress and rest perfusion CMRI to evaluate cardiac involvement in SSc patients with no cardiac symptoms. A previous study has demonstrated that combining stress perfusion and DE MRI could be useful to evaluate cardiac involvement more accurately than each approach separately\(^1,2\).

Nevertheless, stress echocardiography remains the preferred method in clinical practice to analyse regional ventricular function because of its high accuracy, versatility, availability and relatively low cost. Comparisons between stress echocardiography and stress cardiac MRI showed a superiority of cardiac MRI\(^3,4\). Superiority of cardiac MRI over echocardiography was more evident in patients with low image quality at echocardiography\(^5\). Introduction of steady-state-free-precession (SSFP) sequences and parallel imaging has improved spatial and temporal resolution. Acquisition time has been reduced to 6-7 s or less for each slice, thus improving regional kinetic analysis and ventricular exploration during pharmacological stress studies\(^6,7,8,9,10\).
Methods and Materials

**Patients.** Study population consisted of 10 consecutive female patients (mean age 49.5) with SSc as defined by the American Rheumatism Association classification criteria\(^{11}\), and recruited with the collaboration of Rheumatology Clinic at San Salvatore Hospital, in L'Aquila, Italy. We chose to include only women to avoid the potential confounding effect of gender in this small pilot study. 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 in all patients \(^{12}\). Exclusion criteria were pregnancy, evidence of cardiomegaly on chest radiography, symptoms of heart failure, coronary artery disease, systolic blood pressure < 90 or > 150 mm Hg, heart rate < 50 or > 130 bpm, pulmonary arterial hypertension, severe valvular heart disease, atrial fibrillation, diabetes mellitus, hyperlipidemia, dyslipidemia, past and current history of smoking, history of bronchoconstriction, contraindication to MRI, hypersensitivity to gadolinium or adenosine triphosphate (ATP), and past or current treatment with prostacyclin for digital ulceration. Informed consent was obtained from all patients.

**MR Imaging.** CMRI was performed using a 1.5-Tesla superconducting whole-body system. An eight-channel phased-array superficial coil was used. Images were gated with the cardiac cycle using a retrospective vectorcardiogram (VCC). Cardiac synchronisation was performed with four nonmagnetic electrodes placed on the left anterior hemithorax and connected to the console by means of optical fibres. Intravenous access was gained through the right antecubital vein. A three-channel ECG monitor was connected, and pulsoximetry and brachial blood pressure were measured simultaneously. Patients underwent cine-MRI, pharmacological stress and rest perfusion study. Evaluations at rest were performed with Cine steady-state sequences in 4-chamber view and short axis view. Dipirydamole was infused using an automated injector at a constant rate of 0.84 mg/kg body weight per minute, for 6 consecutive minutes. Subsequently, a contrast agent (Gd-BOTPA) was injected (0.05 mmol/kg) to obtain the first-pass perfusion study \(^{13, 14}\); then the same cine steady-state sequences of the baseline study were repeated. After a 10-minute delay, a second dose of Gd-BOPTA (0.05 mmol/kg) was administered and the rest perfusion study imaging was performed (Cine Steady-state sequences in 4-chamber view and short axis view). Each acquisition was obtained during a breath-hold of 6-7 s depending on heart rate. First-pass perfusion was performed using T1-weighted saturation recovery (SR) sequences repeated for 25-30 s for each R-R' or 2R-R' intervals, depending on heart rate, to obtain at least three slices for each acquisition at the apical,
papillary and basal level. First-pass perfusion analysis was obtained on short-axis views after injection of 0.05 µm/kg of gadolinium at a flow rate of 5 ml/s. The acquisition was repeated over 25-30 s after gadolinium injection. Stress evaluation was performed using the same planes of the baseline study.

**MRI Interpretation.** Imaging was analyzed by 2 independent radiologists, blinded to clinical information, and kinetic analysis was performed by a Segment® software analysis. Stress PD lesions, when present, were characterized by distribution as segmental or nonsegmental. Cases of disagreement between the observers resolved by reviewing the images and reaching a consensus.
Results

Characteristics of the 10 enrolled patients are summarized in Table 1 (Fig.1). Patients had a mean age of 49.5 ± 6.4 years at the time of scanning and a mean SSc disease duration of 3.2 ± 3.1 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 8.7 ± 2.7. 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%.

Stress perfusion defects were seen in 4 out of 10 patients (40%)(Fig.2); one of these was found to have a persistent perfusion defect both at stress and rest study (Fig.3). None of the patients demonstrated instead kinetic alterations (video1, Fig.4). The volumetric analysis showed in 2 out of 4 patients (50%) with a stress perfusion defect, RV-EDV= on average 70 ml, and RV-EF= on average 42.5%.

Association of cardiac MRI findings with clinical characteristics of SSc. No clinical characteristic was associated with any MRI finding with the possible exception of digital ulceration, according with litterature¹, in which PD were seen in 75% (3 of 4) of the patients compared to only 20% (1 of 5) of those without this history (prevalence ratio 3.75). Interestingly, in these 3 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. However, owing to our small sample size , this association was not statistically significant.
### Table 1. Clinical and laboratory characteristics of patients with SSc (n = 10).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>49.5 ± 6.4</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Cutaneous subtype, diffuse:limited, n (%)</td>
<td>5 (50):5 (50)</td>
</tr>
<tr>
<td>Total skin score</td>
<td>8.7 ± 2.7</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>3.2 ± 3.1</td>
</tr>
<tr>
<td>History of digital ulcer (including pitting scar), n (%)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Interstitial lung disease, n (%)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Esophageal involvement, n (%)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Fasting plasma sugar, mg/dl</td>
<td>90 ± 5.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132 ± 6.5</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77 ± 6.3</td>
</tr>
<tr>
<td>Smoking (ever and current), n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>180 ± 10.2</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>130 ± 6.4</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dl</td>
<td>50 ± 3.4</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dl</td>
<td>104 ± 10.9</td>
</tr>
<tr>
<td>Framingham 10-year hard cardiovascular risk, %</td>
<td>4 ± 2</td>
</tr>
<tr>
<td>Antitopoisomerase I antibodies, n (%)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Anticentromere antibodies, n (%)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Normal ECG: Q wave (−), arrhythmia (−), block (−), n (%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Ejection fraction on ECE, %</td>
<td>67 ± 2.7</td>
</tr>
</tbody>
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Except where indicated otherwise, values are mean ± SD. ECG: electrocardiograph.

**Fig. 0:** Characteristics of study population

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Fig. 0: Stress perfusion MRI shows a perfusion defect

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**Fig. 0**: Persistent perfusion defect at rest perfusion study

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Fig. 1: Stress cine MRI shows no evidence of kinetic alterations

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Conclusion

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. 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 $^{15,16,17}$. 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.

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. Cardiac involvement is common in SSc. Its detection and histological confirmation are often difficult because of a lack of symptoms$^{18}$. Thus, dipirydamole stress perfusion CMRI could be considered a non-invasive method to evaluate early microcirculatory involvement in the subclinical phase of SSc.

Further studies of this diagnostic tool should be evaluated to discuss its utility and to confirm our results$^{19}$. 
References


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