

Cardiac magnetic resonance in systemic sclerosis patients with cardiac symptoms

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Abstract. – OBJECTIVE: Systemic sclerosis (SSc) is characterized by widespread vascular lesions and skin and internal organs fibrosis, including the heart; all cardiac layers, endocardium, myocardium, and pericardium, may be involved. We report the relevance of cardiac MRI findings in scleroderma patients with cardiac symptoms.

PATIENTS AND METHODS: 50 patients, all fulfilling the ACR SSc criteria (19 with limited and 31 with diffused skin involvement) were evaluated using a 1.5T MR scanner. Images were acquired before and after contrast medium administration; the exams were considered positive with one or more of these findings: enlarged volumes, reduced EF, regional kinetic anomalies, edema, DE or pericardial effusion.

RESULTS: 40 patients (80%) had one or more cardiac abnormalities: 5 patients had myocardial edema; 2 an increased interventricular septum thickness; 22 dilated ventricles or reduced EF; 12 an abnormal regional ventricular motion (2 of these with akinetic segments); 17 a delayed enhancement with different patterns, all without coronary distribution; 22 a pericardial effusion

CONCLUSIONS: Pathologic findings were documented in 80% of the cases confirming a high occurrence of abnormal MR data. Myocardial involvement in systemic sclerosis can be assumed by the presence of multiple pathologic MRI findings. CMR seems to be a valuable tool to identify and assess the presence of cardiac involvement.

Key Words:

Cardiac magnetic resonance, Systemic sclerosis, Delayed enhancement.

Introduction

Systemic sclerosis (SSc) is a disease characterized by widespread vascular lesions and fibrosis of the skin and internal organs including the heart¹. Although cardiac involvement is often clinically occult, myocardial involvement is common in SSc, and when sensitive tools are used, it has

been estimated to occur in up to 100% of SSc patients^{1,2}. The presence of cardiac involvement in SSc is often underestimated and its recognition is important being associated with a 70% mortality at 5 years³. All cardiac layers, endocardium, myocardium, and pericardium, may be involved. This may result in pericardial effusion, atrial and ventricular arrhythmias, conduction system defects, valvular impairment, myocardial ischemia, myocardial hypertrophy and myocardial dysfunction, with/without heart failure^{1,2}.

Cardiovascular magnetic resonance imaging is a safe, useful and noninvasive modality that can be used in assessing myocardial function and it is valuable in detecting cardiac inflammation, edema, necrosis or fibrosis^{4,5}. We aimed to evaluate the presence of MRI findings in a population of SSc patients showing signs or symptoms of cardiac involvement, its role in assessing these patients gaining new insight into pathophysiology and prognosis.

Patients and Methods

Between 2008 and 2016 we studied 50 patients aged between 21 and 79 years old (mean age 50.2±15.2 years), 43 females and 3 males. All the patients fulfilled the American College of Rheumatology SSc criteria⁶. 19 (38%) patients showed limited and 31 (62%) diffuse skin involvement. Mean disease duration was 73.0±70.2 months.

All patients enrolled showed signs or symptoms of cardiac involvement.

Cardiological symptoms as angor, hypotension, palpitation, syncope were present in 20 (40%) cases, dyspnea in 78%, cardiac enzymes elevation in 45 (90%) patients (T troponin 90% and/or CK-MB 70%), EKG-Holter alterations in 48% of the cases.

All patients underwent echocardiography and MRI. In selected cases, coronarography or endomyocardial biopsy was performed (7 patients).

Magnetic resonance imaging was performed using a 1.5 T machine (Achieva, Philips Medical Systems, Eindhoven, the Netherlands) with gradient field strength of 66 mT/m using a 5 elements cardiac coil. Cardiac synchronization was obtained with 4 nonmagnetic electrodes placed on the left anterior hemithorax and connected to the console using optical fibers. Electrodes were placed on the chest so to maximize the R wave and to obtain a good EKG triggering. Cardiac gating was performed with a vectorcardiographic approach.

Cine sequences were obtained at baseline along the vertical and horizontal long axis views, with a segmented cardiac gated multiphase steady-state free-precession (SSFP) sequence, with the following parameters: repetition time (TR) shortest, echo time (TE) shortest, flip angle 60°, slice thickness 8 mm, no interslice, image matrix 320X224, FOV 32 cm.

For edema evaluation, we performed a multislice multiplanar unenhanced triple IR TSE T2-weighted sequence TR = 2RR TE = 100 FOV = 32 cm SENSE P_{reduction} value = 2.

Subsequently, all subjects received an intravenous bolus injection (0.05 mmol/kg; infusion rate 5 ml/s) of gadolinium chelate (Gadobutrol, Gadovist, Bayer Pharma AG, Berlin, Germany).

First-pass perfusion images were acquired using multislice fast saturation recovery gradient in the short axis, obtaining a series of 60 images, one for a heartbeat: TR = 2.4 TE = 1.2, flip angle = 60° P_{red} value = 1.5.

During the sequence, breath-hold was maintained for as long as possible to the patient.

Immediately after the first-pass acquisition, a second bolus of contrast medium (0.05 mmol/kg, infusion rate 2 ml/s) was delivered to obtain a total dose of 0.1 mmol/kg of Gd-chelate.

Short axis views cine imaging was then performed using SSFP acquisitions and parallel imaging: repetition time (TR) shortest, echo time (TE) shortest, flip angle 60°, slice thickness 8 mm, no interslice, image matrix 320X224, FOV 32 cm, P_{red} = 1.5.

About 10-12 min after contrast injection we performed a Look-Locker sequence, to define the optimal inversion time to null the myocardial signal for delayed enhancement. We found optimal T1 values between 180 and 320 ms.

Delayed enhancement (DE) short and long axis images were acquired 12-15 min after the injection of contrast with a fast gradient echo inversion-recovery – 2 dimensional sequence: TR shortest, TE shortest, flip angle 15°, turbo factor =

25 slice thickness 8 mm, no interslice gap, matrix 320x240, FOV 32 cm.

We also performed a 3D acquisition with 3 slabs of 360x360x42 mm TFE = 27 TR shortest, TE shortest flip angle = 15° P_{red} = 1.5

Post processing was performed using dedicated software on a CVI 42 console (Circle Cardiovascular Imaging Inc., Calgary, Canada)

End-diastolic and end-systolic volume, ejection fraction, stroke volume were calculated for both ventricles by defining the endocardial contour on end-diastolic and end-systolic short-axis cine images. The volume of individual slices was subsequently summed to calculated volumes in end-diastole and end-systole, as well as stroke volume and ejection fraction (EF).

The presence of LV and/or RV dilatation was defined as an increased indexed LV and/or RV end-diastolic volume compared with available normal values provided by Hudsmith et al⁷. These were also used to define an impaired LV or RV EF.

The myocardium was divided into 17 segments according to the American Society of Echocardiography standardized myocardial segmentation.

All studies were analyzed by two experienced readers and all the findings expressed as a consensus among the readers. Readers were blinded to all clinical information related to the patients.

For each segment regional myocardial function was visually defined as normal, hypokinetic, akinetic or dyskinetic; the presence of subendocardial or transmural perfusion defect at rest was reported.

Edema and delayed enhancement areas were visually identified as high signal intensity present in the same myocardial segment in at least two different imaging planes. Also, endocardial and epicardial regions of interest (ROI) were manually contoured in the analysis software and edema and DE areas were confirmed by the analysis software as regions with signal intensity 2 standard deviation greater than the mean SI of the normal remote myocardium.

DE identified in the different segments was classified as sub-endocardial, mid-myocardial and transmural and its pattern as linear or patchy.

Statistical Analysis

Statistical analyses were performed using MedCalc for Windows, version 11.4 (MedCalc Software, Ostend, Belgium). The morphological and functional data CMR were evaluated using descriptive statistics and expressed as mean ± SD. Comparisons were made with independent *t*-test, and nonparametric tests (Mann-Whitney, or Fi-

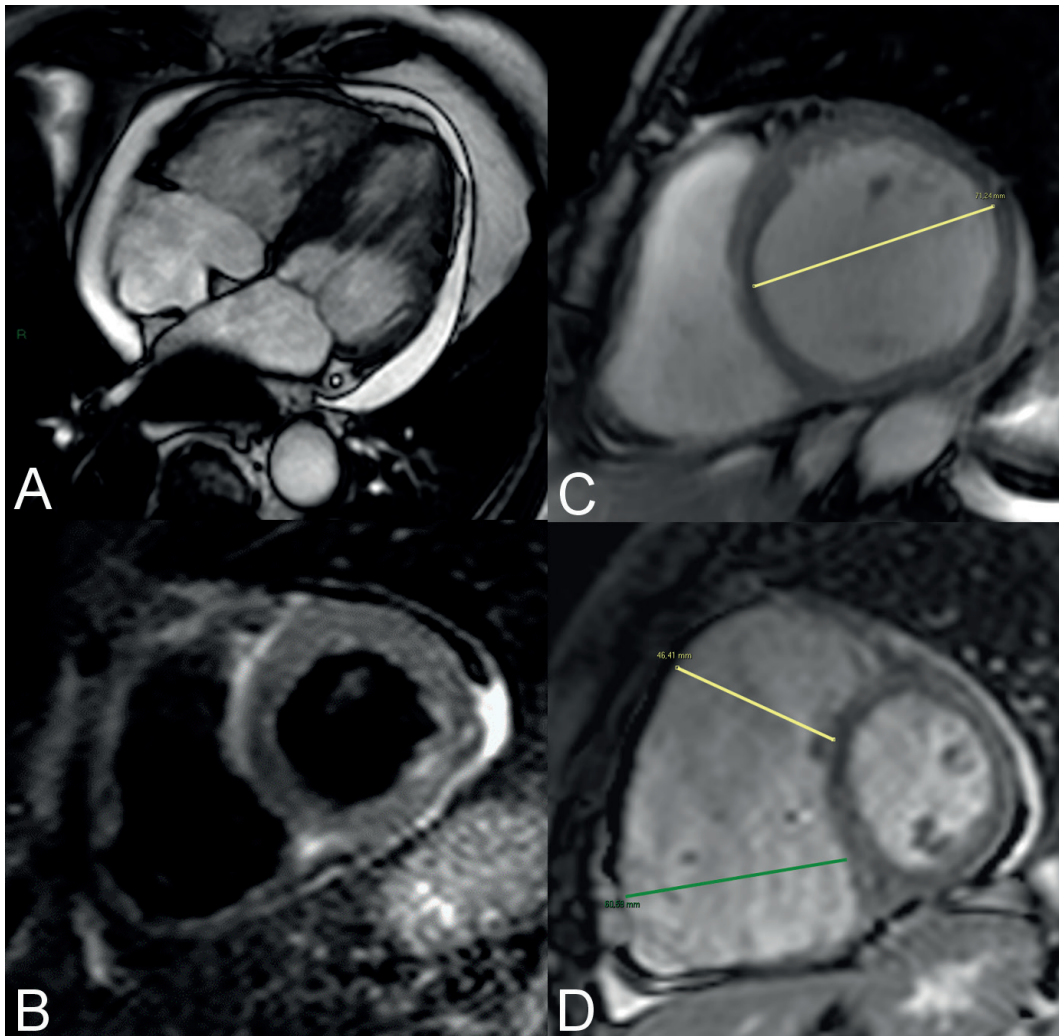


Figure 1. MR findings in patients with SSc. *A*, Pericardial effusion. *B*, Edema. *C*, LV dilatation. *D*, RV dilatation.

sher's exact test). Pearson's correlation was used to study the association of the MRI indices with continuous variables. Statistical significance was considered at $p < 0.05$.

Results

Myocardial involvement is frequently observed in systemic sclerosis. CMR can detect both morphological and functional abnormalities (Figure 1).

On T2-STIR images, myocardial edema was identified in 5/50 patients.

LV and RV wall thickness was within normal limits. Only in two patients, we found an increased interventricular septum thickness.

We classified ventricular volumes and function according to the published criteria by Hudsmith et al⁷ that consider sex- and age-related differences, and we compared our data to those criteria.

We excluded 1 case ($F < 35$ years) as we considered the exam of non-sufficient quality.

We found the following left ventricle volumes: LVEDVI = 81 ± 21 ml/m², LVESVI = 33 ± 18 ml/m², RVEDVI = 82 ± 20 ml/m², RVSVI = 35 ± 18 ml/m²; LVEF was $61 \pm 10\%$, and RVEF $58 \pm 12\%$.

Abnormal regional ventricular motion (LV and RV hypokinesia, akinesia or dyskinesia) was present in 12/50 patients, of these 2 had a kinetic segments.

We only performed rest perfusion finding a rest perfusion defect in 2 patients with subendo-

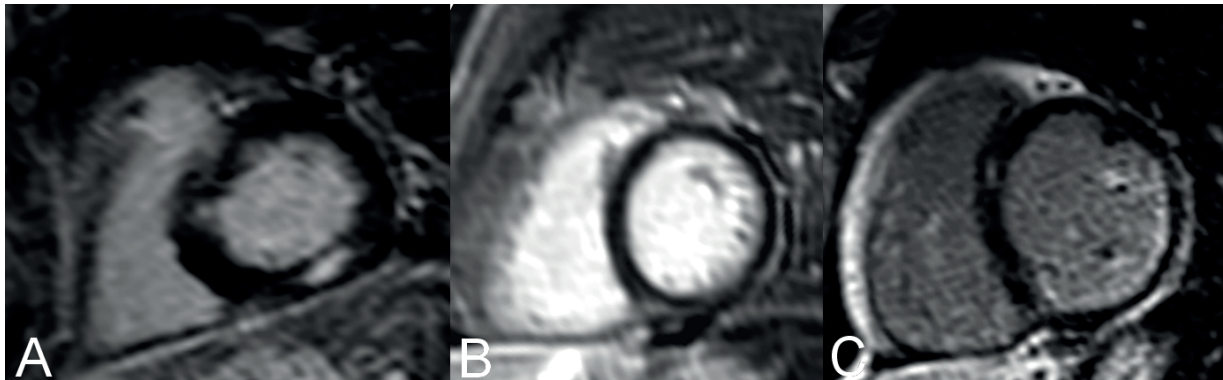


Figure 2. Patterns of delayed enhancement on short axis images. *A*, Intramural. *B*, Subepicardial. *C*, Subendocardial.

cardial DE. Among the 50 patients of our study, the myocardial late enhancement was detected in 17 (34%). Enhancing myocardium weight was between 0.6 and 13.8 g (mean 3.6 g).

DE has been classified according to its distribution pattern (Figure 2).

A centroparietal linear or patchy enhancement sparing the subendocardium and epicardium was present in 7 patients (12 segments, 0.6-3.6 g mean 1.6 g); a diffuse subendocardial pattern was seen in 4 cases (15 segments 3.8-13.8 g mean 8.2 g), in 3 patients DE was subepicardial (9 segments, 0.6-3.5 g mean 2 g, in one patient transmural (3 segments 7,1 g). In 2 cases (3 segments) intramural and subepicardial patterns were combined (1.4-1.6 g mean 1.5 g).

In all studies, DE areas showed a non-coronary pattern.

Two cases were excluded: in one it was not possible to acquire the late enhancement sequence, in the other one the image quality was judged inadequate.

We found DE in 42 segments, mainly in basal (21/42) and middle (20/42) ones. The subendocardial enhancement was seen in the inferior (2/42 segments) posterolateral (7/42 segments) and anterolateral (5/42 segments) wall. Intramural enhancement prevailed in the septum (9/42), inferior and posterior wall (4 segments). Subepicardial (9 segments) and transmural (3 segments) enhancement was present in the inferior and inferoseptal segments.

Sub-endocardial involvement showed no correlation with any coronary artery distribution: these patients underwent coronary angiography that excluded coronary stenoses.

A pericardial effusion was present in 22/50 patients. 16 patients (32.0%) had minimal peri-

cardial effusion while 6 patients (12%) had a circumferential pericardial effusion >5 mm.

Discussion

In the present study, we evaluated CMR findings in a subgroup of 50 SSc patients positive for cardiac signs or symptoms.

Previous MRI studies in literature examined patients non selected for signs of cardiac involvement⁸⁻¹¹ or SSc patients without cardiac symptoms^{12,13}. Mavrogeni et al¹⁴ studied retrospectively (among 246 connective disease patients) 30 SSc patients with a negative echocardiogram and typical or atypical cardiac symptoms; in another paper patients with recent onset of left bundle branch block¹⁵.

Pathologic findings were documented in 80% of the cases (40/50 patients) confirming a high occurrence of abnormal MR data. MRI was positive for the presence of any of the considered parameters (enlarged volumes, reduced EF, regional kinetic anomalies, edema, DE or pericardial effusion) in 40/50 patients (80% $p < 0.0001$).

The combination of the different findings was frequent (more than one in 42% of positive cases). In categorical analysis of pathologic CMR findings, 3 patients (6%) had positive findings in six categories (edema, DE, pericardial effusion, LV dilatation, LV reduced EF, LV kinetic abnormalities, RV dilatation, RV reduced EF), 2 patients (4%) in five, 4 patients (8%) in four, 4 patients (8%) in three, 3 patients (6%) in two categories, and 24 patients in one category (48%).

Edema has frequently been observed in patients with SSc^{9,14,16}. Myocardial edema was identified in 5/50 of our patients; due to the higher water content

of the wall, edema determines a T2-STIR hyperintensity⁷. It indicates acute myocardial injury associated either with inflammation, such as during myocarditis, or with myocardial infarction.

Edema increases the gadolinium distribution space and causes delayed enhanced areas¹⁷; it can be identified simultaneously or early before the appearance of DE lesions. All our patients with edema showed DE in the same segments.

T1 mapping, which is highly sensitive to myocardial water and is superior to T2-weighted imaging in detecting myocardial edema, was not available at the time of this study.

We found an increased IV septum thickness in two patients: a similar finding was ascribed to compensatory hypertrophy by Schicchi et al¹¹.

LVEDVI resulted above normal limits⁷ in 6/49 patients; LVESVI was increased in 2/49 cases; LVEF was below the normal in 12 patients.

RVEDVI resulted above normal limits⁷ in 3/49 patients; RVESVI was increased in 3/49 cases; RVEF was below the normal in 10 patients. 24% of the patients had regional kinetic anomalies.

Increased LV and RV volumes are a known finding in SSc^{9,16}. In both acute and chronic SSc myocardial damage, an important finding is a presence of kinesis abnormalities and function impairment^{3,9}.

RV dilatation occurred independently from pulmonary hypertension, as already described by other authors^{9,18}. Right heart dysfunction is common in SSc patients⁹.

Cojan Minzat et al¹⁹ stressed the role of MRI in the early and accurate detection of right ventricle impairment.

LV regional anomalies were described by Hachulla et al⁹ in 16/52 patients, Schicchi et al¹¹ (4/26 patients), and Sano et al¹⁰ (3/50 patients). Kobayashi et al¹³ underlined the high prevalence of regional dysfunction in patients with both diffuse and limited cutaneous types of SSc

Although we performed only a basal perfusion study our findings of a defect in only 2 patients is significantly lower from what previously reported by Schicchi et al¹¹ who found first-pass perfusion defects in 6/26 patients or by other studies where stress perfusion was performed^{20,21}

Prevalence of DE (34%) and its different patterns (subendocardial, intramural, subepicardial) match previous works in the literature.

Delayed enhancement may allow us to better define and understand the kind of damage in SSC, sometimes giving us a clue about the pathogenesis as they correspond to the areas of myocardial

necrosis, fibrosis or myocarditis as shown by comparison with histopathology¹³.

In SSc, the fibrosis may involve the immediate subendocardial layer; subendocardial DE is indicative of subendocardial vasculitis¹⁴ or results from the general microvascular vasospastic mechanism that is thought to play a key role in this disease²².

Intramural/subepicardial DE not following the distribution of coronary arteries suggest myocarditis^{15,16}. Reports of SSc patients with coexisting myocardial disease and myositis suggest an association between myocarditis and peripheral myositis may exist. The fibrotic process may be secondary to chronic cardiac inflammation³.

Previous studies reported different fibrotic patterns in SSc.

Subendocardial, midwall, and subepicardial DE were described by Hachulla et al⁹ (In 2/52 patients subendocardial, in 8 mid-wall, in 1 subepicardial), by Mavrogeni et al¹⁴ (subendocardial pattern in 5/45 patients, subepicardial or intramural DE pattern in 13/45 patients) and by Pieroni et al¹⁶ subendocardial 1/7, linear midwall 1/7, subepicardial and patchy midwall 4/7 patients). A subendocardial pattern was also found by Sano et al¹⁰. Other studies did not report subendocardial enhancement.

Di Cesare et al¹² found DE with a linear or nodular midwall pattern in 25/58 patients; Tzelepis et al⁸ a linear midwall pattern in 24/36 patients, in 7 cases associated to a patchy nodular pattern. Kobayashi found DE in 4/15 SSC patients¹³.

We found no difference in the presence or type of DE between patients with limited and diffuse disease.

In our study patients with DE had lower left and right ventricular ejection fractions in comparison with patients without DE (LVEF = 65±13.1 vs. 54±13 $p=0.0013$; RVEF = 60.3±9.6 vs. 52.4±15 $p=0.03$). The most accurate cutoff point discriminating patients with and without LE appeared to be 61% for LVEF and 58% for RVEF.

Seven (14%) of the 50 patients deceased. Of these 4 (23.4%) had DE, notably two with subendocardial pattern.

We found a high prevalence of pericardial effusion (44%). This is known to be frequent in SSc^{3,18} having been found in 6/7 patients by Pieroni et al¹⁶, in 10/52 patients by Hachulla et al⁹; in 7/50 patients by Sano et al¹⁰.

MRI data were not compared to echocardiography. This technique, however, is poorly specific and cannot distinguish between possible

etiologies of myocardial dysfunction with accuracy and cannot perform tissue characterization to detect early silent lesions²³.

Patients that underwent myocardial biopsy showed active/acute myocarditis in 6/7 cases and borderline/chronic myocarditis in 1 case¹⁶. At CMR, DE was present in 6 of these patients. In all cases, DE areas had a non-coronary distribution, with subepicardial and patchy midwall pattern in 4, linear midwall pattern in 1, and subendocardial distribution in 1. Hyperintense areas on T2-weighted images, indicative of myocardial edema and associated with DE areas, were documented in 2 patients. Three patients showed an enlargement of the right ventricle, associated with global contractile dysfunction in one case. A mild to moderate pericardial effusion was detectable in 6 patients.

Conclusions

Recurrent vasospasm and inflammation may cause myocardial involvement in SSc, contributing to the development of myocardial fibrosis and the varied clinical manifestations of myocardial disease in SSc, which include asymptomatic systolic or diastolic dysfunction and clinically overt heart failure²⁴. MR allows early detection of cardiac abnormalities in SSc patients, including inflammation, perfusion defects, and diffuse or localized fibrosis²³.

Our study indicates that myocardial involvement in systemic sclerosis can be assumed in the presence of multiple pathologic MRI findings: abnormal regional ventricular motion (LV and RV hypokinesia, akinesia dyskinesia) reduced LV-EF or RV-EF; positive LGE, left or right ventricular dilatation, pericardial effusion; MR findings were documented in 80% of the cases. CMR diagnosis of myocardial involvement in SSc requires increased attention to subtle findings¹⁸.

Patients without fibrosis didn't have major cardiac events. Subendocardial DE is due, at least in part, to microcirculation damage¹⁵; this pattern was associated in two of four patients with death.

MRI positivity may suggest to perform a biopsy to confirm cardiac fibrosis although this technique is limited by its invasive nature and its low sensitivity^{25,26}.

CMR appeared to be a valuable tool to identify and assess the presence and extent of cardiac involvement.

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Conflict of interest

The authors declare no conflicts of interest.

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