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Advances in the Diagnosis of Multi-organ Involvement in Systemic Sclerosis: A Focus on Magnetic Resonance Imaging

Attila Feher,[1,2] Francesco Del Galdo,[3] Sven Plein[4]

[1] Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

[2] Department of Radiology and Biomedical Imaging, Yale University School of Medicine, New Haven, CT, USA

[3] Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

[4] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

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Corresponding Author:

Attila Feher, MD PhD

Section of Cardiovascular Medicine

Department of Internal Medicine

Yale University School of Medicine

P.O. Box 208017, Dana 3

New Haven, Connecticut 06520, USA

Phone: 203-785-5005

Fax: 203-737-1026

E-mail: attila.feher@yale.edu

Abstract

Purpose of review: Systemic sclerosis (SSc) is a rare chronic multisystem autoimmune disease characterized by endothelial dysfunction, tissue hypoxia and diffuse organ fibrosis. Magnetic resonance imaging (MRI) provides a radiation free approach to noninvasively assess the key manifestations of SSc in multiple organs. The purpose of this review is to summarize recent advances in MRI techniques to provide diagnostic and prognostic information in patients with SSc.

Recent findings: MRI can probe processes that play a key role in the development of SSc related complications including neointima proliferation, fibrosis and hypoxia. Feature tracking and parametric mapping MRI can detect cardiac involvement at the subclinical level. Contrast-free MRI angiography with Digital Artery Volume Index (DAVIX) assessment allow comprehensive assessment of hand involvement. T1 mapping and BOLD imaging can assess SSc effects on skeletal muscle and lung MRI is becoming a key method for imaging of interstitial lung disease. As a new exciting application, the sodium content of the skin can be quantified by ^{23}Na MRI reflective of glycosaminoglycan content.

Summary: Recent advances in magnetic resonance imaging provide a unique opportunity to study the key pathophysiologic processes and clinical manifestations of SSc in multiple organs noninvasively which can pave the way for the development of effective therapies.

Keywords: systemic sclerosis, magnetic resonance imaging, parametric mapping

Introduction

Systemic sclerosis (SSc) or scleroderma is a rare (~240 cases per million adults) chronic multisystem autoimmune disease (1). The underlying pathophysiology includes a highly variable autoimmune process, endothelial injury with loss of capillaries and small vessel narrowing, with subsequent tissue hypoxia, and a deregulated fibroblast activation leading to diffuse organ fibrosis (2). Magnetic resonance imaging (MRI) is a non-invasive imaging modality that generates high-resolution anatomical images and offers a unique opportunity to study multiple processes involved in the pathophysiology of SSc. MRI offers high tissue contrast that can be manipulated to highlight different tissue characteristics. For example, T1 mapping MRI generates pixel-wise maps representing the T1 relaxation times of tissues and when combined with (T1-shortening) gadolinium-based contrast agents can be used to estimate the extracellular volume fraction (ECV) of tissue. Myocardial fibrosis typically exhibits increased native T1 values and increased ECV compared to normal myocardium. T2 mapping, on the other hand, is sensitive to variations in water content making it suitable to quantify and track inflammation and/or edema. Other MRI methods relevant to the assessment of SSc include MR angiography (MRA), using either exogenous or endogenous contrast methods, quantitative blood flow imaging and metabolic assessment with MR Spectroscopy. This review aims to provide an overview of some of the recent MRI developments and their potential application to investigating the most common organ manifestations of SSc (Figure 1).

Evaluation of digital vasculopathy by MRI

Hand involvement is very common and contributes to 75% of global disability in SSc patients (3). Several studies have used hand MRI to evaluate musculoskeletal structures and joint disease in SSc (4-6). In these studies, MRI detected frequent abnormalities including synovitis, bone edema and erosions. A higher number of erosions was detected by MRI (63%) when compared

to X-ray (28%) in 82 consecutive SSc patients with clinical signs and symptoms of joint involvement (4).

Growing evidence indicates that vascular damage is a primary event in SSc pathogenesis (7). Eventually the vascular process affecting capillaries, arterioles and even large vessels leads to reduced blood flow and tissue ischemia. As a consequence an estimated 50% of SSc patients experience DUs (8) of which up to 20% may experience digital amputation (9).

While the association between digital vascular abnormalities and DU has been well documented, until recently only a handful of studies have performed digital artery evaluation by contrast enhanced MRA. The challenge with contrast MRA is to acquire high-resolution images in a short time (acquisition time must be short enough to prevent venous contamination of the arterial anatomy) and with an adequate signal-to-noise ratio while covering the whole region of interest. Allanore et al. demonstrated that over 90% of 38 SSc patients had at least one digital artery that could not be visualized beyond the first phalanx and over 60% of SSc patients had at least 4 poorly visualized arteries by contrast MRA (10). In addition, in this study nearly all patients (92%) showed abnormal venous return suggesting a systemic vascular problem. A study by Asadourian et al. evaluated the radial and ulnar arteries and the superficial and deep palmar arches by contrast enhanced MRA in 21 SSc patients with digital ischemia. In SSc patients the ulnar artery was significantly smaller than the radial artery and was found to be occluded in 46% (11). It is important to mention that these studies required contrast administration and many times a contrast free technique is desirable, to reduce scan time and burden to patients and healthcare systems.

Given these concerns, recently multiple groups have applied non-contrast MRA techniques to study vascular abnormalities in SSc. Lim et al. applied a three-dimensional MRA technique (electrocardiographically gated variable flip angle fast spin-echo) for successful imaging of hand arteries with detection of vascular caliber changes in different temperature settings (12). By adjusting the flip angles of the radiofrequency pulses, this technique provides optimized signal

intensity and contrast resulting in enhanced image quality of MRA images. An early study by Krause et al. compared time-of-flight, rephased/dephased, and contrast enhanced MRA to digital subtraction angiography in a limited number of subjects (13). The study concluded that time-of-flight MRI, which provides contrast between the vasculature and stationary tissues by inducing blood inflow effects, had a high sensitivity for detecting angiographically occluded digital arterial segments whereas rephased/dephased MRA and contrast enhanced MRA were inferior to contrast angiography and time-of-flight MRA. Digital Artery Volume Index (DAVIX) is a novel MRI technique employing time-of-flight MRA. DAVIX of the single finger is defined as the ratio of digital artery volume over the total finger volume (expressed as a percentage) (14). DAVIX of the dominant hand is calculated as the mean DAVIX of the four fingers of the dominant hand after excluding the thumb. Recently, data from a large single center study involving more than 200 patients reported that DAVIX can discriminate patients with or without DU and can predict the onset of new DUs (14). In the exploratory cohort, DAVIX was significantly lower in patients with history of DU or active DU when compared to patients without DU (median DAVIX of 0.34% [IQR: 0.16–0.69%] versus 0.65% [IQR: 0.42–0.88%]). In addition, during the 12-month follow-up time those patients who developed new DU had lower baseline DAVIX when compared to those who did not (median DAVIX of 0.23% [IQR: 0.10–0.66%] versus 0.65% [IQR: 0.45–0.91%]). DAVIX negatively correlated with SSc duration, nailfold capillaroscopy pattern, and baseline modified Rodnan skin score and positively correlated with the diffusing capacity of carbon monoxide, suggesting a putative value as imaging surrogate outcome measure of systemic vascular involvement.

Cardiac evaluation by MRI

SSc affects the heart both directly (primary heart involvement) and as a consequence of other organ effects (primarily lung disease causing pulmonary hypertension). The pathophysiology of primary heart involvement in SSc includes the combination of all 3 main pathogenetic processes

recognized in SSc, such as inflammation, fibrosis and microvascular disease (15). All these processes can be evaluated by cardiac MRI, using a combination of parametric mapping, contrast enhanced and first pass perfusion methods, sometimes before cardiac involvement is clinically manifest. This makes cardiac MRI a unique tool for the detection of and screening for cardiovascular involvement in SSc. The recently published guidance by the World Scleroderma Foundation/Heart Failure Association on the assessment of SSc–associated primary heart involvement suggests that a screening cardiac MRI can be considered in asymptomatic SSc patients even without history of previously documented heart involvement (16).

Tissue fibrosis is the hallmark feature of SSc and in the heart, it can be quantified using T1 mapping MRI (17). T1 mapping is particularly useful in SSc as it can identify diffuse fibrosis as it does not rely on regional differences in tissue composition. Multiple groups have demonstrated increased myocardial T1 values and ECV in patients with scleroderma when compared to controls, indicating diffuse subclinical myocardial fibrosis (18, 19). A recent study evaluating 110 SSc patients demonstrated that native T1 values but not ECV was predictive of cardiovascular mortality (20).

Primary heart involvement in SSc has also been associated with focal myocardial fibrosis or scarring, which is assessed by the MRI method of late gadolinium enhancement (LGE). The method is based on the fact that the distribution volume of the clinically used gadolinium-based MRI contrast agents is exclusively extracellular and any tissue with an expanded extracellular space such as scar and focal fibrosis retains more contrast agent than normal myocardium. Using dual inversion recovery MRI methods, these areas of focal scar/fibrosis can be visualized with high tissue contrast and spatial resolution. Several studies have reported on the presence of focal myocardial scar in SSc. Dumitru et al. detected progression of SSc heart involvement by serial cardiac MRI in 31 SSc patients without cardiovascular disease during the 33-month follow-up (IQR: 17-37 months) with ~10% of patients showing increase in the extent of focal scar by LGE MRI, however otherwise stable indices including left ventricular ejection fraction, ECV and

myocardial perfusion reserve (21). It is important to emphasize that LGE assessment detects only focal fibrosis while diffuse fibrosis, which is frequently observed in SSc, can only be detected with parametric mapping. Therefore, T1 mapping should be included when assessing patients with SSc with cardiac MRI.

Myocardial inflammation can be detected using T2 weighted MRI methods, which are sensitive to the water content of tissue. Together with T1 weighted methods and LGE, T2 weighted imaging forms part of the diagnostic criteria for myocarditis, which is common in patients with SSc and is associated with poor prognosis (22). Patients with SSc may show focal enhancement on T2-weighted imaging or an increase in the myocardial to skeletal muscle T2 ratio. However the use of this ratio is problematic in disease processes where the skeletal muscles are affected such as SSc. T2 mapping provides absolute T2 relaxation times and is therefore becoming the preferred method for the detection and quantification of myocardial inflammation. A study by De Luca et al. showed that by incorporating T2 mapping in the diagnostic criteria of SSc associated myocarditis with the revised Lake Louise criteria, the sensitivity improved from 53% to 90% (23). A study by Meloni et al. detected similar left and right ventricular end diastolic volumes, ejection fraction, left ventricular mass index, frequency of positive late gadolinium enhancement in SSc patients with or without abnormal T2 relaxation time (24).

Microvascular involvement can be evaluated by cardiac MRI using first pass myocardial perfusion imaging combined with absolute myocardial blood flow quantification. Prior studies with positron emission tomography myocardial perfusion imaging demonstrated impaired myocardial flow reserve in patients with SSc (25) and demonstrated prognostic value (26). In line with this, a study by Dumitru et al. incorporating MRI blood flow quantification in SSc revealed lower stress myocardial blood flow (1.9 mL/min/g [IQR: 1.4-2.6 mL/min/g] vs. 2.6 mL/min/g [IQR: 2.0-3.6]) and lower myocardial perfusion reserve (1.9 [IQR: 1.6-2.4] vs. 3.0 [IQR: 2.0-3.6]) in 83 SSc patients when compared 44 healthy controls (19).

Finally, cardiac MRI is the reference standard for the evaluation of the left and right-ventricular systolic function. It therefore plays an important role in detecting overt heart failure and monitoring progression of heart failure in patients with SSc. However, ejection fraction does not represent all myocardial properties and often remains normal in subclinical cardiac disease with imperfect correlation with adverse cardiovascular outcomes (27). Feature tracking cardiac MRI is an emerging tool for the assessment of myocardial deformation providing incremental data about ventricular systolic function. Multiple studies have evaluated feature-tracking strain by cardiac MRI in patients with SSc (28-32). These studies confirmed impairment in left ventricular (28-30) and right ventricular feature tracking strain (28, 29). A recent study by Feher et al. demonstrated marked reduction in survival in SSc patients with both impaired left ventricular global longitudinal strain and late gadolinium enhancement (32). Recent studies provided new evidence that right atrial strain could also provide prognostic value for predicting mortality in SSc patients (33, 34).

Imaging peripheral muscle involvement

Peripheral muscle involvement in SSc include myositis or non-inflammatory myopathy, both of which may be evaluated by MRI. A recent small study showed elevated lower extremity ECV in 12 SSc patients with or without suspected myopathy compared with 10 healthy controls (23 ± 10% vs. 11 ± 4%, p=0.04) suggesting presence of diffuse fibrosis in peripheral muscle of SSc patients (35). Interestingly this study showed no significant difference in the skeletal muscle native T1 relaxation times between the two groups, however T1 relaxation time was modestly higher in SSc patients when compared to controls (1396 ± 56 msec vs. 1387 ± 42 msec, p=nonsignificant). This study also demonstrated correlation between ECV and creatine-kinase levels and higher ECV was detected in those SSc patients with suspected myopathy.

Blood oxygen level-dependent (BOLD) MRI is a noninvasive technique that can be used to evaluate dynamic changes in skeletal muscle oxygenation in response to reactive hyperemia. The registered signal intensity during BOLD MRI is based on relative changes in paramagnetic

(weakly attracted by an external magnetic field) deoxyhemoglobin and diamagnetic (weakly repelled by an external magnetic field) oxyhemoglobin in skeletal muscle microvasculature, an increase in blood oxygen saturation results in an increase in T2*-weighted BOLD image signal intensity. A recent study investigated calf muscle hypoxia in response to cuff occlusion with blood oxygenation level dependent (BOLD) MRI in 12 SSc patients and 12 healthy volunteers, found good correlation between BOLD T2* signal and transcutaneous oxygen pressure with BOLD MRI showing good correlation with oxygenation deficits in patients with SSc (36). In a separate report Partovi et al. also found a good correlation between calf muscle BOLD T2* signal and microperfusion measured by laser Doppler flowmetry in SSc patients (37).

Skin involvement

Skin involvement is a prominent manifestation of SSc. MRI has not been routinely used for the evaluation of skin fibrosis. Recent studies speculate that sodium content of the skin can be quantified by ^{23}Na MRI which can be reflective of glycosaminoglycan content (38). Unlike traditional hydrogen-based MRI, which primarily images water and fat, ^{23}Na MRI directly images the distribution and concentration of naturally occurring sodium atoms in the body to create images. Dissimilar to hydrogen-based MRI which focuses on anatomical details, ^{23}Na MRI aims to quantify sodium concentration and distribution within tissues. ^{23}Na MRI has been used to quantify increased sodium content in the skin (forearm and dorsal lower leg) of patients with SSc compared to controls (27.2 ± 5.6 vs. 21.4 ± 5.3 mmol/L) (39). In addition, the sodium content was found to be higher in fibrotic versus nonfibrotic areas of skin in SSc patients (26.2 ± 4.8 vs. 19.2 ± 3.4 mmol/L). Skin sodium amount correlated well with changes in modified Rodnan skin score on 12-month follow-up (R^2 = 0.68).

Lung involvement

Interstitial lung disease (ILD) is one of the major causes of mortality in patients living with SSc (40). While CT remains the gold standard technique for evaluation of ILD, it has been recently proposed that dedicated chest MRI sequences could provide a radiation-free alternative for routine monitoring chest CTs (41, 42). Imaging lung parenchyma by MRI has been a challenge for decades for multiple reasons: 1) the lung parenchyma has low proton density leading to weaker signal 2) abundant sharp air/soft tissue interfaces causing susceptibility artifacts 3) motion artifacts due to constant respiratory motion. To overcome these limitations groups have employed ultra-short echo time sequences which use extremely short echo times (often less than one msec) allowing the capture of signals from tissues with rapidly decaying signals (such as lung tissue). Recent studies demonstrated excellent correlation between extent of ILD measured by CT or MRI in SSc patients and good correlation between ILD extent by MRI and forced vital capacity (41-43). In addition, higher lung T2* signal has been detected in connective tissue disease related ILD in comparison to healthy controls (1.25 ± 0.23 vs. 0.95 ± 0.08 msec, p=0.0019) and significant correlation was detected between lung T2* relaxation time and pulmonary function test results including forced expiratory volume (r=-0.40, p=0.04), vital capacity (r=-0.68, p=0.0001) and diffusing capacity for carbon monoxide (r=-0.73, p<0.0001) (44). Oxygen enhanced MRI utilizes the paramagnetic effect of high concentration of inhaled oxygen promoting longitudinal relaxation of nearby protons, and has been suggested to be useful for the evaluation of regional ventilation and gas exchange within the lungs (45). Ono et al. demonstrated that oxygen enhanced MRI was comparable to thin-slice CT images to estimate disease severity in ILD (46).

Conclusions

Current and emerging MRI methods can probe processes that play a key role in the development of SSc related complications including vasculopathy, fibrosis and hypoxia. Cardiac evaluation by feature tracking strain imaging and parametric mapping including T1 and T2 mapping can detect cardiac involvement at the subclinical level. Contrast-free MRI angiography

with Digital Artery Volume Index (DAVIX) assessment, skeletal muscle T1 mapping and BOLD imaging and ILD evaluation by lung MRI are among other emerging new clinical applications and other methods such as ^{23}Na MRI of the skin offer exciting prospects for future research.

Key points

- MRI can probe processes that play key role in the pathogenesis of SSc related complications including vasculopathy, fibrosis and hypoxia.
- Cardiac evaluation by feature tracking strain imaging and parametric mapping including T1 and T2 mapping can detect cardiac involvement at the subclinical level.
- Contrast-free MRI angiography with Digital Artery Volume Index (DAVIX) assessment, skeletal muscle T1 mapping and BOLD imaging and ILD evaluation by lung MRI are among the emerging new applications.
- As a new exciting application, the sodium content of the skin can be quantified by ^{23}Na MRI reflective of glycosaminoglycan content.

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Figure Legend

Figure 1. Novel MRI techniques for the evaluation of systemic sclerosis. Abbreviations: MRI: magnetic resonance imaging, DAVIX: Digital Artery Volume Index, BOLD: Blood oxygen level-dependent MRI, ECV: extracellular volume